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Methodological Challenges in Pharmacoepidemiological Studies of Opioid Consumption

Thesis for the degree of Philosophiae Doctor

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Norsk Sammendrag

Avhandlinga har studert to metode utfordringer når man skal gjøre studier på bruken av opioider. Hvordan måle forbruket av legemiddelet best mulig, og hvordan gjenkjenne faste brukere av opioider. I tillegg er sosioøkonomien til faste brukere av opioider studert.

Måten man måler forbruk av legemidler er viktig i legemiddelepidemiologien. Ofte har man ikke informasjon om dosering for den enkelte pasient og man må brukes en gjennomsnittlig dose i stedet. Verdens Helseorganisasjon har et mye brukt system kalt definerte døgndoser (DDD). Her er DDD for hvert legemiddel definert som den vanligste daglige vedlikeholdsdosen hos voksne med den vanligste indikasjonen for legemiddelet. Når man skal studere bruken av opioider er bruken av DDD utfordrende. Siden opioider er smertestillende er det mange ulike tilstander som kan gi et behov for smertestillende. DDD for hvert opioid er bestemt ut fra hvor sterke smerter legemiddelet er tiltenkt å behandle, men doser kan variere mye og det er vanlig praksis å starte med de svakeste opioidene og så bytte til sterkere ved behov. En pasient kan derfor bruke 1 DDD av et svakt opioid og så få byttet behandlingen til 0.5 DDD av et sterkere opioid som da gir en bedre smertelindrende effekt. Når man studerer en populasjon over tid der pasienter både bruker svake og sterke opioider og bytter mellom disse vil DDD systemet kunne få problemer med å beskrive hva som foregår. I denne avhandlinga har vi regnet ut den relative styrken til hver opioid sammenlignet med morfin og sett at denne tilnærminga gir andre resultater enn bruk av DDD alene. Vi har konkludert med at bruk av denne equianalgetiske tilnærminga er et verdifullt tillegg til bruk av DDD alene.

I de siste tiårene har kroniske smertetilstander i økende grad blitt behandlet med opioider. Denne faste bruken av opioider kan gi pasienter mindre smerter og bedre livskvalitet, men den kan også fore til et problematisk opioid bruk, avhengighet og dårligere livskvalitet. Langvarig bruk av opioider er lite studert i den norske befolkningen. I Norge er 80% av opioidresepter på kodein-paracetamol, bedre kjent som paralgin- og pinex forte. Dette er ulikt andre land som USA der sterkere opioider brukes mye mer. Siden bruken av opioider kan variere med smertene og doseringa ikke er kjent så er det utfordrende å måle fast bruk. Vi har utviklet og testet tre ulike definisjoner på

fast bruk av opioider, disse bruker mengde opioider i løpet av et år fra første resept ble utlevert, antall resepter utlevert og om disse er fordelt ut over hele årsperioden.

En halv prosent av Norges befolkning bruker opioider tilsvarende minst en gang per dag over en periode på 365 dager. Denne gruppa ble nærmere studert og sammenlignet med opioidbrukere som ikke er faste brukere. Faste brukere hadde lavere utdanning, lavere inntekt, var oftere uten arbeid og uføre og oftere skilt/separert enn de ikke-faste brukerne.

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I would also like to thank all my friends. I value you all immensely. You have always made my days better when I am frustrated over the thesis and the slow process of publishing papers. Some knows how frustrating a ph.d. can be, others have patiently listened to my complaints. Helge has been my contact with normal life here in Trondheim, and he has had to listen and pretend to be interested in all kind of research details. Mariann started a ph.d. before me and have always been able to give advice and I really have enjoyed our walks and talks and every thing else during the years you stayed here in Trondheim. Helen also deserves a big thank you for reading and correcting my thesis, great job, it really improved the end result!

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Finally I would like to thank my family for always supporting my choices and for being patient when listening to me rambling about my work. I hope I have made you all proud!

English Summary

In pharmacoepidemiology, the way one measures drug use is very important. Since few studies have information about what dose the patient is actually using an average dose is often used. The world health organisation (WHO) has a system of defined daily dose (DDD). DDD is defined as the most common daily maintenance dose for the most common indication in adults and is set by experts. When studying opioids there are extra challenges when using the DDD system. Doses of opioids might vary a lot and the DDD for different opioids are determined by the severity of pain the opioid was initially planned to treat. However the choice of opioid for each patient might change. Patients might start with an weak opioid and switch to a stronger opioid if the weak opioid does not provide sufficient effect. The patient might use an average dose of the weak opioid, or 1 DDD, but might just need 0.5 DDD of the strong opioid for strong pain. Using the DDD system this patient will have seemingly decreased his dose even if the pain is treated more effectively after the switch. In population studies following patients over time, and mixing patients using strong and weak opioids, this was therefore a problem. In this thesis the relative strength of each opioid or equianalgesic ratio was used and the influence on results when using this approach compared with the DDD approach was investigated. It was shown that results might indeed change significantly and that using an equianalgesic ratio to create oral morphine equivalents as a unit of measurement of amounts is a valuable addition to DDD in studies of opioid use.

During the last few decades chronic non-malignant pain has increasingly been treated with opioids. This persistent use of opioids can greatly benefit the patients, but can also cause problems such as problematic opioid use and addiction. The use of opioid analgesics persistently has been poorly studied in populations such as the Norwegian one. In Norway 80% of the volume consumed is codeine-paracetamol, in contrast to the use in the US where stronger opioids such as oxycodone are used more. However it is difficult to determine what is persistent opioid use when using prescription data, since doses might vary greatly between patients and over time. It was therefore necessary to create definitions of persistent opioid use able to capture the different clinical usage patterns and patients switching opioids over time.

About 0.5% of the population in Norway uses opioids in doses corresponding to daily use over a 365 day period. In the thesis this group of patients has been compared with opioid users who had 3 or fewer prescriptions dispensed during 365 days. The association between persistent opioid use and education, income, work status, marital status and immigrant background was analysed. It was found that lower education and income, not working, ethnic Norwegian background and being divorced were associated with persistent opioid use 4 years later.

This thesis has dealt with two important methodological challenges in pharmacoepidemiological studies, namely measuring opioid amounts and defining persistent opioid use. Finally the socioeconomy of persistent opioid users were studied.

Abbreviations

ATC	Anatomical Therapeutic Chemical
CNMP	Chronic Non-Malignant Pain
DDD	Defined Daily Dose
DOPr	Delta Opioid Receptor
HUNT	Nord-Trøndelag health study
IASP	International Association for the Study of Pain
INCB	International Narcotics Control Board
KOPr	Kappa Opioid Receptor
MAP kinase	Mitogen Activated Protein Kinase
MOPr	Mu Opioid Receptor
NOPr	Nociceptin Opioid Receptor
NorPD	Norwegian Prescription Database
NSAID	Non-Steroidal Anti-Inflammatory Drug
OMEQ	Oral Morphine Equivalents
PPSG	Pain and Policy Study Group
UN	United Nations
WHO	World Health Organisation
WTD	Waiting Time Distribution

List of Papers

Paper I:

Choosing the unit of measurement counts: The use of oral morphine equivalents in studies of opioid consumption is a useful addition to defined daily doses.

Svendsen K, Borchgrevink PC, Fredheim OMS, Hamunen K, Mellbye A, Dale O.

Palliative Medicine 2011;25(7):725-32.

Paper II:

Differential patterns of opioid use: defining persistent opioid use in a prescription database.

Svendsen K, Skurtveit S, Romundstad P, Borchgrevink PC, Fredheim OMS.

Accepted in European Journal of Pain. DOI: 10.1002/j.1532-2149.2011.00018.x

Paper III:

Persistent opioid use and socioeconomic factors: a population based study in Norway.

Svendsen K, Fredheim OMS, Romundstad P, Borchgrevink PC, Skurtveit S.

Manuscript

1. Introduction

1.1 Pain

1.1.1 Development of the understanding of pain

The origin of the English word pain is from the Latin word poena, meaning punishment. Pain is also described in the Bible as a result from, and punishment for the original sin committed by Adam and Eve (New International Version, Genesis 3.16-17). From this it is reasonable to assume that it was believed that pain in medieval Europe was seen as divine retribution or as sign of being chosen by God and as such being worthy of the rewards in the hereafter [1,2]. Early treatments for pain differed between cultures, but included prayers, cupping and acupuncture [3]. In ancient Greece, and in the Roman culture, physicians such as Hippocrates and Galen used a vide variety of words to describe different types of pain, both physical and emotional [2]. However the belief that diseases were caused by imbalances in the humoural fluids did not allow any significant understanding of the physiology of pain [3]. Since then the understanding of pain has developed throughout the medical history. Making a leap from ancient times to the 1890's, two competing schools of thought developed. The two directions were mutually exclusive, and researchers were influenced to explain their findings in the light of one or the other of these theories [4]. Neither theory could explain all the experimental and clinical findings. In 1965 in an article in Science, Melzack and Wall, a physiologist and a psychologist, introduced a new theory, the gateway theory of pain [4].

The gateway theory tried, and to a certain extent managed, to reconcile the different paradigms. Melzack and Wall proposed that incoming information from nerve endings was modulated through presynaptic inhibition. This "gateway" would be opened either when the painful stimuli became intense enough or through damage to the inhibiting fibres, creating hypersensitivity to painful stimuli [3,4]. Many specifics of this theory has since been proved wrong, but the idea of pain modulation by central mechanisms and competing stimuli has lead to a more complex understanding of pain [3].

In more recent time research into the transmission and transduction of pain has focused on biochemical and genetic alterations [3,5]. An important concept in recent research is the concept of neural plasticity defined by Woolf as ”the capacity of neurons to change their structure, function or chemical profile via activation, modulation and modification” This then would lead to hypersensitivity and pain [6].

1.1.2 Definition of different pain terms

Pain is inherently quite subjective, this then leads to difficulties in choosing common terms when talking about pain [7]. In the present thesis the most important pain terms to define is chronic and acute pain. The International Association for the study of pain (IASP) defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage” [8]. IASP has not defined chronic and acute pain explicitly but the textbook Bonica’s management of pain has an extensive discussion on the different ways to define these terms [7]. The transition from acute to chronic pain has normally been defined as pain lasting longer than a certain time. Both three and six months have been proposed as a cut-off time and also used as case-definitions in epidemiological studies [9–14] . Another way of separating the two terms is that “pain extending beyond the expected period of tissue healing” can be defined as chronic pain. This definition is more clinically relevant since it is reasonably independent of time and depends on the injury/condition each patient has. This definition, however, is difficult to use for case definition in epidemiology because of the individual time span. Furthermore different definitions have different criteria regarding whether chronic pain is constantly present, present most days or pain that is present several days a week. Finally pain intensity above a certain threshold value is required in order to meet the criteria for the case definition in different epidemiological studies, usually pain intensity >3 on an 11-point scale or “moderate” pain on a verbal rating scale. These definitions of chronic pain are fairly simple, but studies of- and guidelines for- chronic pain will have to use simplistic definitions even though the patients are complex. The American guideline on the use of chronic opioid therapy in chronic non cancer pain (CNMP) uses pain lasting longer than

3 months as their definition [15]. Other guidelines on chronic opioid use for chronic/persistent pain does not explicitly indicate what they define as chronic pain, leaving this to be resolved by the clinicians reading the guidelines [16–18].

Pain can also be classified by its etiology, it can be benign or adaptive, malignancy related, postsurgical or degenerative [19]. The origin of pain influences the prognosis and treatment strategies. Another way of classifying pain is by its mechanism. Physiological pain can be divided into neuropathic and nociceptive pain, and nociceptive pain can be further divided into somatic and viceral pain [19].

1.1.3 Epidemiology of chronic pain.

A large pan-European phone survey by Breivik et al. of 16 countries found that 19% of the population met the three criteria in the case definition of chronic pain: 1) pain lasting for more than 6 months, 2) having had pain during the last month and 3) pain at least twice per week. The country with the lowest prevalence reported was Spain with a prevalence of 12% whereas the prevalence of 30% in Norway was the highest in the study [14] . This number may seem high but also other studies such as one in the US [20], Australia [10], and one from Canada [21] have reported similar prevalence. A Danish study reported a 20% prevalence of pain lasting at least 6 months [22], while an English study of self-reported pain lasting longer than 3 months reported an almost 50% prevalence [11]. In a recent study using the Nord-Trøndelag health study (HUNT) 29% had chronic pain defined as lasting more than 6 months with at least moderate pain the last month [9].

A different study also collecting data from a survey reported that 24% of Norwegians had chronic pain lasting longer than 3 months and that 43% used analgesics as treatment for pain, while 31% did not receive any treatment for their pain [13]. Breivik et al. also reported that 31% did not receive any treatment [14]. For about 26% of the pain-sufferers non-drug treatment were reported to have been very or extremely helpful. About half the patients took prescription medicine for pain and NSAIDs (Non Steroidal Anti Inflammatory Drugs) were the

most commonly used prescription drug. Around 15% of pain sufferers in the Breivik study used opioids [14].

1.1.4 Treatment of chronic pain

As our understanding of the multitude of factors affecting pain, and its mechanisms, increase the complexity of pain treatment also increases [3]. Chronic pain cannot always be relieved, and will not always have clear patho-physiological causes. Interdisciplinary chronic pain management has since its introduction in the late 1960's in the US gained increasing evidence for treating severe chronic pain conditions [23]. Cognitive-Behavioural therapy, physical therapy, treatment of co-morbidities such as anxiety and depression are now considered important when treating chronic pain [23]. Pharmacological treatments include the use of NSAID, antidepressants such as the Tricyclic antidepressant amitriptyline, antiepileptics such as gabapentin and pregabalin, as well as the familiar non-opioid analgesics paracetamol and acetylsalicylic acid. For some patients these drugs are not sufficient and opioids are needed to relieve the pain [24–27]. Opioids have been used for a long time and are potent analgesics. Opioid use is the subject of this thesis and opioids will be dealt with in detail in the following chapter of the introduction (chapter 1.2).

1.2 Opioids

1.2.1 History of opium and opioids

Opium has been known to be used for medical reasons for thousands of years, the ancient Sumerians described the poppy as the plant of joy[28]. A study of the use of opium in antiquity by Hippocratic physicians concluded that it did not seem that the analgesic effect of the poppy was known [29]. In the middle ages the opium containing tinctures called Laudanum was used in Europe for a wide variety of ailments such as cholera [30]. In the poppy there are more than 20 different alkaloids, known collectively as opiates. These include pain relieving chemical compounds such as morphine and codeine, but also compounds with other primary effects such as noscapine (antitussive) and loperamide (antidiarrhea) [28]. The first pure alkaloid isolated was morphine in 1804 by the

German pharmacist Sertürner. Codeine and papaverine were both isolated by the end of the 19th century [30]. In addition to the naturally occurring alkaloids in opium, it is possible to chemically change the naturally occurring compounds to create additional compounds. Heroin is also known as diacetylmorphine, and is produced by a di-acetylation of morphine. This was first done for commercial purposes in 1897 by the German pharmaceutical company Bayer. Heroin, as the brand name was, became a hit for Bayer. Only 13 years after coming to the market Bayer stopped selling Heroin. This happened after the initial reports claiming no addiction and less side effects than both codeine and morphine were disproved. [31]. In more recent times, several more molecules have been synthesised, both semi-synthetic drugs such as oxycodone and hydromorphone, and synthetic drugs such as fentanyl, pethidine and methadone[25,27]. Collectively these drugs, both natural, semi-synthetic and synthetic are called opioids. Opioids are "any drugs with morphine- like effects (analgesic effect) that are blocked by antagonists such as naloxone" (meaning that they work in the opioid receptor system) [25].

1.2.2 Opioids: Policy and regulations

The United Nations' International Narcotics Control Board (INCB) deal with how all issues of opioid production, use, export/import and working against illegal sales and production should be regulated internationally [32]. Locally in Norway a recent debate has been how to treat heroin addicts, with methadone and buprenorphine, or also allowing heroin to be used to persons where all other treatments have failed. This serves as an example of how opioids and the use of them are contentious issues. Historically opium has also been in the centre of important events. The opium wars in the mid 1800's were a result of China wanting to stop the illegal import of opium to their country by the British. This business had exploded in the early 1800's and caused the Chinese a lot of problems. Large sums of silver were being traded with the British with a return of suffering, addiction and a decrease in productivity in China. The yearly sum paid for opium to the British equalled 2.5 times the total government spending of China and between 4 and 12 million Chinese were addicted to opium [33]. The

yearly sale of opium from the British colonies to China reached a staggering amount of 3000 tons per year by the 1840's and the following confrontation between the Chinese and the British led not only to the defeat of China and the opening of many cities to westerners but also the English supremacy of what is now modern day Hong Kong, which was kept as a British colony until 1999. In 1912 the first international opium convention was held by the League of Nations in Hague, and today most countries work against an increase in illegal trade of opioids and have signed the 1961 single convention on narcotic drugs [34]. However, opium is still being produced on a large scale illegally. In Afghanistan, the largest producer of illegal opium in the world, more than 1200 km^2 of the country are being used for opium cultivation. Afghanistan produced 3600 tons in 2010 while the estimated illegal demand world wide of opium is close to 5000 tons. In Afghanistan alone the stockpiles are estimated at 12000 tons, enough to supply the world for 2.5 years [35].

1.2.3 Pharmacology and clinical implications

Opioids work on the opioid receptors throughout the body. These drug-receptor interactions cause both the therapeutically wanted effect of pain relief but also side effects such as constipation, drowsiness, respiratory depression, nausea, and euphoria [36]. There are four main classes of opioid receptors, the MOPr (μ), DOPr (δ), KOPr (κ) and the NOPr receptors. All opioid receptors are G-protein-coupled receptors. The MOPr receptors are responsible for most of the analgesic effects of opioids, but also for a wide range of unwanted effects such as respiratory depression, euphoria, sedation, physiological tolerance and dependence [37]. DOPr receptor activation also causes some analgesic effect but is suspected of having a convulsant effect. KOPr activation provides analgesic effect at the spinal level, as well as sedation, dysphoria and hallucinations (in contrast to MOPr which gives euphoria). NOPr has an anti-opioid effect supraspinal and also gives catatonia and learning impairment [25]. In addition to the immediate response opening potassium channels and inhibiting calcium channels the opioid receptors also activate the Mitogen-activated protein kinase (MAP kinase) most likely leading to long-term adaptive changes of the cells. This is believed to be

important in the development of physical dependence. Since no opioid receptor only provides analgesia it seems impossible to create an opioid drug without major side effects. Also worth mentioning is that in addition to opioids with an agonist/partial agonist effect, full antagonists such as naloxone and naltrexone are also known. Thus an effective antidote to overdoses of opioids is available, an important advantage in medical practice [25,27].

The problem of dependence and addiction.

Patients using opioids for some time develop a physical dependence. This is well known and happens with all opioids [17,38–40]. Dependence is described as having withdrawal symptoms when ending treatment such as unpleasant emotional effects and motivational effects [40]. For some patients problematic opioid use can develop beyond what would be expected from the physical dependence and tolerance. This use is can also develop further into addiction. Addiction is defined by criteria such as impaired control over drug use, compulsive use, continued use despite harm, craving, unsanctioned dose escalation, hoarding and sale of opioids, altering of prescriptions, and unapproved use of other drugs [41–43]. These are all somewhat subjective and clinical criteria and different addiction definitions have led to different estimates of prevalence in the range of 3 to 50% [39,40,44–46]. These definitions include several behavioral patterns that cannot be evaluated in a study based on data from a prescription database. This applies for criteria such as an overwhelming focus on opiate issues during consultations, craving, sale of opioids etc.

1.2.4 Guidelines for chronic opioid therapy in CNMP

As seen earlier chronic non-malignant pain (CNMP) has a high prevalence in developed countries.

There is clearly a need for efficient treatment of CNMP. A minority of chronic pain patients will need treatment with opioids and for these patients different guidelines have been developed. There is an European guideline from 2003 [17], as well as an American guideline from 2009 [15], a British from 2010[18], a Canadian from 2010 [47] and a Norwegian therapeutic guideline from 2008 [48]. Further

guidelines exist for specific patient groups such as the elderly [16] and cancer patients [49]. Below the four most recent general guidelines have been summarized [15,18,47,48].

The guidelines all acknowledge the need for opioids to treat some chronic pain patients. However, an opioid trial should be conducted to see if the benefit outweighs the side effects and the possible negative long term effects [15,18,47,48]. It is also important to record the patient history and evaluate the risk for misuse, abuse, addiction, problematic opioid use [15,18,47,48]. Patients should receive written information and agree beforehand what the goals, expectations and potential side effects are as well as criteria for termination of opioid treatment [15,48]. Benzodiazepines should be tapered of if the patient receives this kind of drugs [47,48] and opioid treatment should be initiated with the lowest possible doses [15,18,47,48]. The Norwegian guideline gives some specific advice on possible start-up doses and also recommend long acting, strong opioids to patients with newly acquired pain with a clear patho-physiological origin and when pain is expected to be long-term and strong [48]. The American guideline does not give any recommendations on the use of long-acting vs. short-acting opioids [15]. In terms of follow-up all guidelines agree that close monitoring is important, and that benefit/harm has to be continuously evaluated [15,18,47,48]. When reaching certain doses extra care is needed, dose thresholds recommended are 200 mg [15,47] or 120-180 mg [18] of morphine or equivalent. Injectable opioids should be avoided [18] and specifically for the Norwegian guideline when doses of weak opioids reach 120 mg for codeine and 150 mg for tramadol a switch to long-acting strong opioids should be considered [48]. Opioid rotation can be tried if lack of effect or unacceptable side effects occur [15]. Comedication with other analgesics should be considered when appropriate [18,48]. Care should be taken to follow-up patients with frequent dose escalations [15]. While most guidelines state that high risk patients with a history of drug abuse and psychiatric problems generally should not receive opioids for chronic non-malignant pain [15,47,48] the British guideline makes a point of stating that there are no right or wrong patients, but that special care needs to be taken when prescribing opioids to high risk patients [18].

1.3 Pharmacoepidemiology

Epidemiology as a science is relatively new. It is possible to trace the first epidemiological studies back to the 19th century. However, as a scientific body it has only started to grow and systematise itself during the last 50 years [50]. Pharmacoepidemiology is a field even more in change, with the initial focus on adverse drug reactions (ADR) and drug utilisation now also branching into health outcome studies and cost-benefit analyses [51]. Pharmacoepidemiology can be defined as "the study of the use of and effects of drugs in large numbers of people". This definition highlights three major differences between pharmacoepidemiological studies and clinical studies.

1. "Large number of persons:" While clinical studies always will have limitations on what is a feasible population to study the effect of a drug in, pharmacoepidemiology does not have this limit. It means that serious and rare ADRs can be studied in a pharmacoepidemiological study, while this is rarely possible in clinical studies [52].

2. "The study of the use:" Pharmacoepidemiological studies are observational; it is the study of the use of drugs as they happen or have already happened. This means that the researcher cannot design studies as a clinical researcher can. This leads to less rigid control over potential biases and confounding and will always make causality hard to establish.

3. "People" not "patients": Pharmacoepidemiological studies do not interfere with real world use. It captures the use without any clinical study enhanced patient follow up, exclusion of co-morbidity and restrictions on age.

Pharmacoepidemiological studies are therefore an essential addition to clinical studies in order to study real world use and also to study research questions that might be unethical to address in a clinical study.

1.4 International studies of the use of opioids

1.4.1 Data from the International Narcotics Control Board

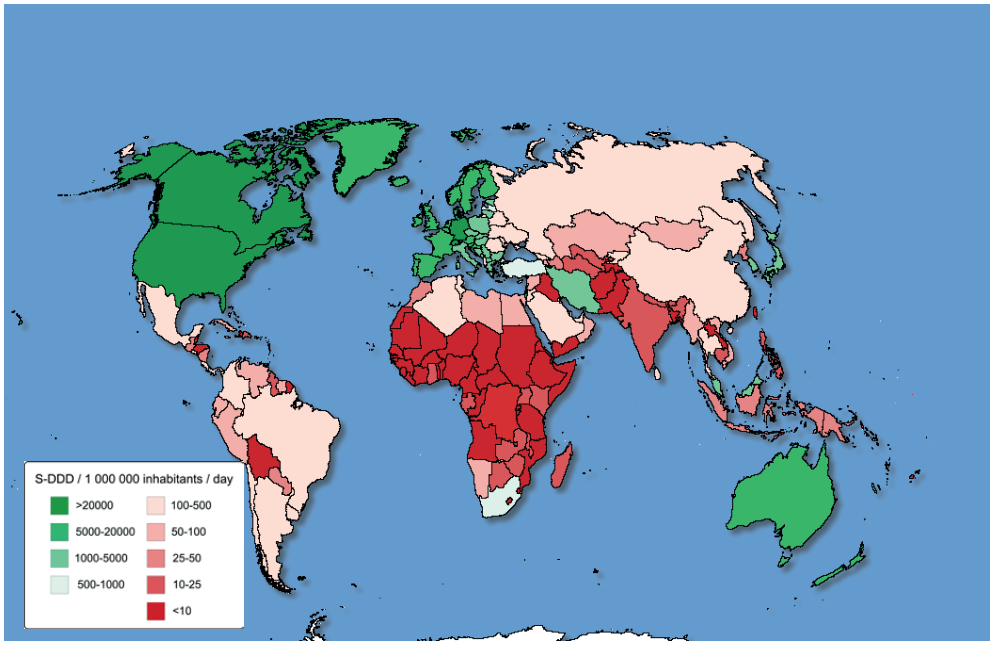

Figure 1 World Map of number of daily doses consumed per 1 million inhabitants per day

All UN nations report their use of opioids to the INCB and have done so since 1968 [32]. Even if the data are aggregated and reported by governments as weight in kilos of each opioid the INCB in their yearly reports include information on use converted into the more comparable S-DDD per 1000000 inhabitants per day. The S-DDD is a simplification of the WHO DDD system. The difference is that while the DDD system includes a daily dose for each administration form the S-DDD will be a single dose per substance since this is the only data available to INCB. Having used INCB data from the most recent technical report [53] a map of the world has been created (figure 1). The Pain and Policy Studies Group (PPSG), a WHO collaborating centre for Pain Policy and Palliative Care, has converted

historical INCB data into mg morphine equivalents per capita and have created a Gapminder like solution for visualising these data [54] By using this solution it is possible to see country wise historical trends in opioid use. The use of opioids internationally has increased steadily during the last few decades [53]. However, there are large differences between Countries as seen in figure 1. The use of opioids are mostly in countries in Europe and North America, for instance these countries consume 90% of all morphine with only 17% of the world population [53].

The country with the highest opioid consumption in the world (USA) uses about 50000 times more opioids per inhabitant than the countries with the lowest consumption (African countries). This difference is growing year by year. The increasing use of opioids in USA and Canada only started around 1985 as shown in the PPSG chart in figure 2. Commonly used opioids in the US include hydrocodone, fentanyl, oxycodone and methadone. Morphine accounts for less than 5% of the consumption. Hydrocodone seems to be by far the most used opioid, accounting for 40% of the INCB statistical daily doses [53]. The Canadian consumption of the different opioids is on the same level as in the US, with the exception of hydrocodone having almost no use in Canada. Hydrocodone is not included in the PPSG data and is not shown in figure 2. With hydrocodone included USA would have been significantly higher than Canada.

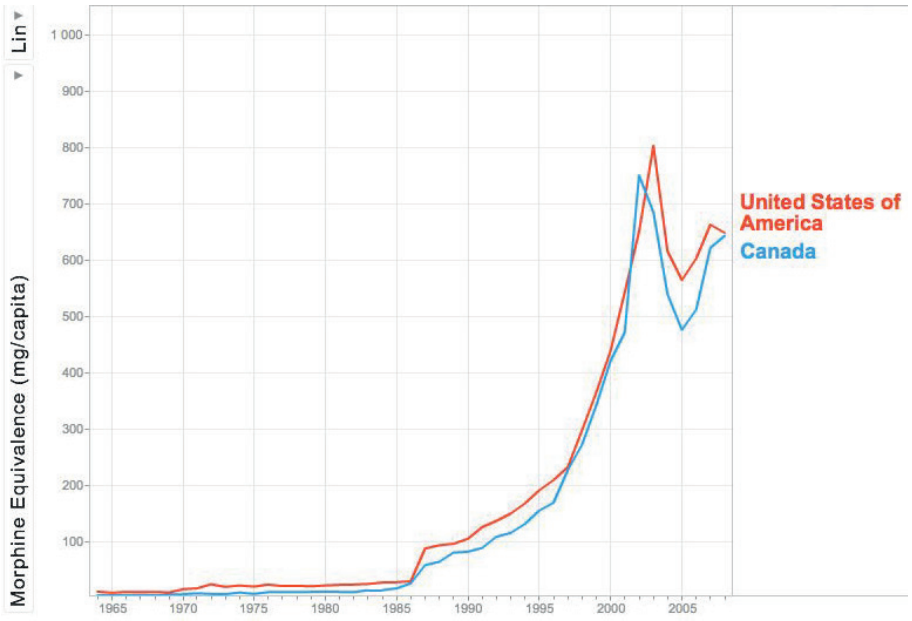

Figure 2 Historical data on opioid use in North America

In Europe, the other region with high use of opioids, there are large differences between countries. Denmark seems to follow USA and Canada with the same increasing use starting in 1986, while the INCB reported opioid use in countries like Germany and Spain started to increase later, around 1995. Eastern European countries have a low consumption of opioids. Analyses based on INCB data on which opioid is most commonly used, have to be performed with caution. While it is known that the consumption of opioids in Norway is dominated by codeine [55], the data from the INCB show almost no use of codeine in Norway [53]. What the INCB data tell us is that fentanyl accounts for a large share of the opioid consumption in most of countries with highest opioid consumption. In Germany, Belgium and Austria the use of fentanyl is even higher measured in S-DDD per inhabitants than in the US. Furthermore the top three countries in oxycodone consumption are the three Scandinavian countries, whereas buprenorphine is used extensively in Belgium and the UK. Other than that, the use from country to country varies widely and no clear pictures emerge based on the INCB-data.

In the rest of the world, opioid consumption in general is low. The exceptions are the consumption in Australia, New Zealand, and in a few Asian countries/territories such as Japan, South Korea, Malaysia and Hong Kong. In Africa only South Africa uses opioids in amounts above 10 mg/inhabitant per year, or about 2-5% of the use in northern Europe and North America.

1.4.2 International pharmacoepidemiological studies

North America

There is an increasing use of opioids in USA: a longitudinal study of prescriber data showed that the frequency of opioid prescribing increased from 1992 to 2001 in patients seeing primary care physicians [56]. The number of consultations at primary care physicians that included prescribing an opioid increased from about 4% in the early 90s to about 6% in 2001. At the same time the frequency of NSAID prescribing and paracetamol prescribing were decreasing or stable, indicating that the increase in opioid prescribing was not associated with a general increase in prescribing of analgesics [56]. Another study of office visits in 1980 and 2000 showed a doubling of the proportion of visits that included the prescribing of an opioid for chronic pain in the 20 year period. During the same period NSAIDs for chronic pain only increased by 16% [57]. There has also been an increase in long-term opioid use in the US. From 1997-2006 the annual prevalence of long term opioid use defined as use longer than 90-120 days in patients enrolled in two large health care plans doubled from 2.0-2.5% to 4-5% [58]. In a telephone survey study from Utah an estimated 20.8% of adult population had received a prescription for opioids the preceding year [59], and about 30% of these opioid users reported that the use was for chronic pain. A phone survey of chronic pain in Kansas estimated that about 4% of the population used opioids to treat chronic pain [20]. These studies show that estimating the true prevalence of opioid use in the US is difficult; the only thing that seems to be certain is that there is an increasing use and that several percent of the adult population uses

opioids long term for chronic pain. There is also a study in Washington State Workers compensation system indicating that while the increase in the number of opioid prescriptions from 1996 to 2002 was not very large there had been a shift towards stronger opioids and higher doses [60].

Canada has several large well known administrative databases usable for pharmacoepidemiological studies. The oldest is the Saskatchewan's health databases started in 1975 and covering about one million inhabitants in the province of Saskatchewan [52]. However there is a reported lack of large scale surveys and studies [61]. In a relatively small but representative phone survey in 2001, 22% of persons with chronic pain (prevalence 29%) were current users of opioids. This means that 6.5% of the population received opioids [21], however 2/3 of these patients used codeine, in sharp contrast to the INCB data from Canada. In a study in the province of Quebec, 15% of their over 400000 persons aged 65 years and older had an opioid prescribed in a year (2001-2002), 60% of these elderly users received a codeine-paracetamol combination, with an average dose of 1.7 DDD/day. Strong opioids were given with an average dose between 0.39 and 0.67 DDD/day [62].

Europe

A study of nine western European countries [63] showed that the use per person was lowest in Italy and Portugal and highest in UK with Norway, Ireland, Belgium, Germany, and the Netherlands in between. This study used wholesale data in 2003, but included only four different opioids: morphine, fentanyl, codeine and tramadol. The study also showed whole-sale prices and fentanyl costs were rising and reached 80 millions euro in 2003 for the nine countries in the study, with the cost of morphine at just over 20 million. In another study of seven different countries also using wholesale data, a large discrepancy between INCB reported data and national whole-sale data from 2002 was seen. Using whole-sale data the 5 Nordic countries had the highest consumption per inhabitant, much higher than Germany and the Netherlands. These differences were much larger than when using INCB data, where Germany had a higher

consumption compared to Norway, Sweden and Finland [64]. In a follow-up study the trends in the Nordic countries were studied from 2002 to 2006. Finland, Denmark, Norway and Iceland showed an increasing use, while Sweden had a decrease. The increase in Norway and Denmark was mostly due to an increasing use of oxycodone, while the increase in Finland was due to slight increases in fentanyl, oxycodone and codeine and in Iceland an increase in oxycodone and tramadol. In Sweden the decrease was due to a strongly decreasing use of dextropropoxyphene and a slight decrease in the use of codeine. Sweden also had an increasing use of oxycodone in the 5 year period [65].

Most European countries have no national prescription databases, and few have had such databases for more than a few years. This limits the knowledge of data on number of patients using opioids. However, Denmark has had a large regional database since the 1990's and this makes Denmark a country where a lot is known about drug consumption in the population. For opioids an early study from 1995 used whole-sale data to study the trends in opioid consumption from 1981 to 1993. The study shows the same increase around 1985 as the INCB data discussed above, and it reveals that this increase is due to an almost 4000% increase in morphine consumption as well as an 450% increase in methadone, the introduction of buprenorphine and a doubling of the ketobemidone consumption during the study period [66]. In 2008, 6.8% of the population in Denmark had at least one prescription of opioids dispensed. The most commonly dispensed opioid was Tramadol, dispensed to over half of the opioid users in 2008. Oxycodone was the most commonly dispensed strong opioid, dispensed to about 1.2% of the population in 2008. Ketobemidone had its highest consumption in 1993-1994 and has since then decreased to about 40% of the 1994 amounts consumed. In 2008 ketobemidone dispensing had a one year periodic prevalence of about 0.5%. Morphine consumption has stayed fairly stable between 1994 and 2008 with a yearly prevalence of around 0.6%, while fentanyl and buprenorphine have increased and were in 2008 each used by about 0.4-0.5% of the population [67]. Several other registry studies have also been conducted studying the opioid consumption in cancer pain patients [68–70]. These

studies have shown that about 30% of the opioids consumed in Denmark are consumed by cancer patients and that this group comprises around 15-20% of opioid users[67,70]. Finally in a national representative survey study of chronic pain, the total prevalence of regular opioid use was calculated to 3% in the population aged 16 years and older, and the majority (2.2%) was regular use by patients reporting chronic pain lasting 6 months or longer [22].

Other country specific studies also exist in countries such as Spain[71], Finland [72,73] and Slovakia[74]. The Spanish study has looked at national data on amounts and found the consumption of opioids to have increased from 0.3 DDD/inhabitant/day in 1992 to 4.4 DDD/1000 inhabitants/day, a 1400% increase. For the opioids methadone, morphine, oxycodone, pethidine, tilidine and fentanyl the increase was 1200% from 0.1 to 1.2 DDD/1000 inhabitants/day. Tramadol is the major weak opioid used at 2.75 DDD/1000 inhabitants/day [71]. The study provides no information about the number of users, so at least some of the increase could be related to increasing average doses rather than an increase in the number of patients treated. In Finland, a Finnish interview study of elderly community-dwelling persons from 75 years and older reported that 7.3 percent used weak opioids as needed and 2.3 percent used weak opioids daily in 2004. Almost no use of strong opioids were reported, only 0.3% used strong opioids as needed [72]. However, a prescription registry study of elderly people with Alzheimer in Finland showed that 3% had at least one prescription dispensed in 2005 of the strong opioids morphine, oxycodone and fentanyl [73]. In Slovakia, wholesale data were used in the same way as in Spain and the use was at 3.41 DDD/1000 inhabitants/day in 2002, an increase of 140% in 5 years. Tramadol dominated the use at 2.61 DDD/1000 inhabitants/day, with fentanyl as the most sold strong opioid at 0.4 DDD/1000 inhabitants/day [74]

Studies from Norway will be described in more depth and detail in chapter 1.5.

Rest of the world

With the limited use of opioids in the rest of the world, a Pubmed and Embase search for pharmacoepidemiological studies of opioids in Australia, New Zealand and South Africa were conducted without any relevant studies found.

1.5 Pharmacoepidemiological studies of opioids in Norway

Norway has had high-quality statistics on wholesale level since the 1970's [75]. However, these data could not be used to, on an individual level, estimate prevalence or incidence, but only to tell the drug volume that has been sold per year and average this out to all persons and measure the drug use as number of DDD/inhabitants/year. This allowed very precise estimates of increase over time, but it could not determine whether this increase was due to higher prevalence of opioid use or a change in consumption patterns leading the same number of users using higher doses.

Table 1 Studies using the NorPD and dealing with opioid use.

	Authors	Title	Year
1	Eggen AE, et al.*	Use of codeine analgesics in a general population. A Norwegian study of moderately strong analgesics [76]	1994
2	Dybwad T, et al.*	Control of prescriptions of B-preparations. A registry study of B-preparations in Oslo and Akershus [77]	1994
3	Engeland A, et al.	Risk of road traffic accidents associated with the prescription of drugs: A registry-based cohort study [78]	2007
4	Bramness J, et al.	Benzodiazepine prescription for patients in opioid maintenance treatment in Norway [79]	2007
5	Bachs L, et al.	Repeated dispensing of codeine is associated with high consumption of benzodiazepines [80]	2008
6	Skurtveit S, et al.	Benzodiazepine use in all alcohol consumers predicts use of opioids in patients 20 years later--a follow-up study of 13,390 men and women aged 40-42 years [81]	2008
7	Fredheim O, et al.	Prescription Pattern of codeine for non-malignant pain: A pharmacoepidemiological study from the Norwegian Prescription Database [82]	2009
8	Skurtveit S, et al	Introduction of low dose transdermal buprenorphine – Did it influence use of potentially addictive drugs in chronic non-malignant pain patients [83]	2009
9	Bachs L, et al.	The risk of motor vehicle accidents involving drivers with prescriptions for codeine or tramadol. [84]	2009
10	Skurtveit S, et al.	Benzodiazepines predict use of opioids – a follow-up study of 17074 men and women [85]	2010
11	Fredheim O, et al.	Increasing use of opioids from 2004 to 2007 – Pharmacoepidemiological data from a complete national prescription database in Norway [55]	2010
12	Skurtveit S, et al.	Nicotine dependence predicts repeated use of prescribed opioids. Prospective population-based cohort study [86]	2010
13	Fredheim O, et al.	Prescriptions of opioids to children and adolescents; a study from a national prescription database in Norway [87]	2010
14	Fredheim O, et al.	Prescription of analgesics to patients in opioid maintenance therapy: a pharmacoepidemiological study [88]	2011
15	Fredheim O, et al.	Opioid switching to methadone: a pharmacoepidemiological study from a national prescription database [89]	2011
16	Handal M, et al.	Use of prescribed opioid analgesics and co-medication with benzodiazepines in women before, during, and after pregnancy: a population-based cohort study [90]	2011
17	Log, T, et al.	The association between smoking and subsequent repeated use of prescribed opioids among adolescents and young adults--a population-based cohort study [91]	2011
18	Log, T, et al.	Dispensing of prescribed analgesics in Norway among young people with foreign- or Norwegian-born parents [92]	2011
19	Skurtveit S, et al	To what extent does a cohort of new users of weak opioids develop persistent or probable problematic opioid use [93]	2011
20	Ineke Neutel C, et al.	Polypharmacy of potentially addictive medication in the older persons-quantifying usage. [94]	2011
21	Nordbø A, et al.	Low-dose transdermal buprenorphine - long-term use and co-medication with other potentially addictive drugs [95]	2011

*: Pre NorPD studies

1.5.1 Early pre-NorPD studies

In the 1990's the increasing use of computers in pharmacies made it possible to conduct the first studies using prescription data. A study of prescription data in all pharmacies in the counties of Oslo and Akershus in 1994 was conducted in order to get a picture of how many prescribers prescribed large amounts of weak opioids and benzodiazepines [77]. Longitudinal analyses were not possible as only birth date was used, not a unique identifying number. However the age of patients was known making it possible to estimate the number of DDD per inhabitant in the counties per month in different age groups. This is the first example of prescription data being used for this purpose in Norway.

Even if this is an old study of prescribers it is so far the only study which has investigated which doctors prescribe large amounts of potentially addictive drugs in Norway. The study found that the prescribers who prescribed the highest number of prescriptions on average prescribed 16 prescriptions per day, and that a mere 30 doctors prescribed 13% of the total volume of these drugs in Oslo and Akershus. At the time there were 4000 physicians registered in the two counties. Over half of these 30 doctors had no medical speciality, 29 of 30 were men and about 30% were aged 40-49 years. Little has been done in more recent times, and with the possibility to follow both prescribers and their patients over time this is an interesting area for future research.

Another study from 1994 was a study conducted in Tromsø using data from all the pharmacies in the town [76]. This is the first pharmacoepidemiological study of all patients using opioids in a certain area of Norway. The study looked at the use of controlled opioids, meaning codeine-paracetamol, pentazocine and buprenorphine (this has later been reclassified to the strictest regulatory class; the narcotic drugs). It is a proto-study using a lot of the techniques recently employed in national NorPD studies. The main findings were that 9.2% of women and 6.5% of men in Tromsø used codeine in a year. Results were also adjusted in regards to age and gender to Norway's population. An estimated 8.9% and 6.8% for women and male respectively received codeine in a year when adjusted. When looking at amounts 17.2% of female users and 29.1% of male users received more than 50 DDD per year, (equalling 200 tablets). Very

few codeine users received more than 365 DDD in a year only 0.6% of the population (34 users of a total of 5306). The study also looked at prescribers though not as thorough as the Oslo-Akershus study. In Tromsø 10 prescribers prescribed 1/3 of the town's consumption of codeine. Tromsø at the time had 52000 inhabitants. Interestingly 24 out of the 34 users using more than 365 DDDs per year received one or more prescriptions from one of these 10 prescribers. Finally it was reported that 85% of users received one or two prescriptions of codeine.

In general the lack of information about number of users has led to perhaps an overestimation of use and fear of opioid use. An example of this is an article from 2004 called "Problem forte - is paracetamol-codeine combination rational?"[96]. It discusses the pharmacology of Paralgin Forte and Pinex Forte the two Paracetamol-codeine containing drugs in Norway. In the introduction wholesale data stating that Norway use 12.9 DDD/1000 inhabitants/day in 2002 is used, and if every Norwegian used opioids each person would on average use 15-20 tablets of Paracetamol-Codeine per year. Using average amounts like this was the best way of describing the total consumption at the time, but later studies using patient data from the NorPD have been able to describe the actual prescription pattern with regard to the number of users and individual yearly doses.

1.5.2 Norwegian Prescription Database studies

There has been a some studies using the NorPD in very specific sub-populations such as Opioid maintenance patients [79,88] and individuals in road traffic accidents [78,84]. These studies, while interesting, are not very relevant for the present thesis dealing with opioid consumption in the general population. In 2008-2009 the first studies looking at the prescribing patterns of specific opioids were published. One study on the introduction of low dose buprenorphine patches in Norway [83] and two studies on the paracetamol-codeine combination [80,82]. The Codeine studies studied all persons that had received at least one dispensed prescription for codeine in 2005 and 2006, excluding those who received it reimbursed for palliation. In 2006 the prevalence was 7.3% for males and 9.3% for females [80]. Incident users were 58% of the study population, incidence defined as not having any codeine dispensed the previous year [82]. 2.5%

received more than 365 DDD per year, while 58% received only one prescription of codeine [82]. There is a steady increase in the prevalence of persistent use when stratifying the population into 10 years age group. The only exception is in the very old (90 years old and older), however a significant proportion of these persons are in nursing homes and will not receive prescriptions to be dispensed at pharmacies. The highest one year periodic prevalence is in the 80-89 year-olds, with a prevalence of around 15%. In children the prevalence is very low and in young adults aged 20-29 the prevalence is less than 6% [82]. In patients receiving more than 120 DDD of codeine-paracetamol 50% co-medicated with more than 100 DDD of benzodiazepines and/or 15 DDD of carisoprodol. In the group using less than 120 DDD of codeine-paracetamol only 9.6% co-medicated with the same levels of benzodiazepines and/or carisoprodol [80].

The Buprenorphine study [83] is an interesting study since it is the only study in Norway to date to look at an opioid when it is introduced into the market. The study compares patients' opioid use before and after they start using low dose transdermal buprenophine. The majority of the patients who received low dose transdermal buprenorphine had used opioids before, and around 55% continued to co-medicate with short acting opioids and a large proportion of users also used benzodiazepines and/or carisoprodol concomitantly with receiving buprenorphine. Both benzodiazepines and carisoprodol should be used carefully in these patients as they are both potentially addictive and together with opioids increase the risk for over-dosing [47,48]. Also short-acting opioids are not recommended in Norway [48] for chronic pain as previously described in chapter 1.2.4. Recently this study from 2009 has had a follow-up study [95]. This study has seen that only 21% of patients on low dose transdermal buprenorphine received enough patches to be treated for 6 months. Since these are long acting formulations and should be suitable for chronic pain patients this percentage is low. The same high levels of co-medication with both other opioids and benzodiazepines were still seen 2 years after the first study.

Two more studies have followed opioid users over time. In one study new users of weak opioids were followed over 4 years [93] and one study of users having methadone prescribed for pain as part of opioid switching, studied both

their use before starting methadone and how long they continued to use it after having the first prescription of methadone dispensed [89]. When following new users of weak opioids it was shown that only 7% of new users of weak opioids in 2005 received opioids yearly in three preceding years (2006-2007), and only 0.3% used opioids all years from 2005-2007 and more than 365 DDD in 2008 (likely persistent opioid users). About 30% of these likely persistent opioid users also received prescriptions from more than three prescribers and had more than 100 DDD of benzodiazepines in 2008. This study clearly shows that only a very small proportion of new users of weak opioids use opioids for anything else than acute pain. It also shows that a very small minority uses more than 1 DDD/day on average each of three years following their first opioid prescription. One thing worth noting is that the definition of new users is no opioids dispensed in 2004. A one-year wash out period is likely to be too short to accurately determine who are opioid naïve users[97] but it should be enough to identify a new episode of pain requiring opioid treatment.

The other study following users over time has looked at a much smaller population, patients switching to methadone in order to improve pain control [89]. The study studied both patients with cancer pain and patients without cancer pain, and excluded everyone who had received methadone mixture or buprenorphine tablets used for opioid substitution therapy. In total 173 cancer patients received methadone tablets and 163 non-cancer patients received methadone as tablets only during the time period of 2004-2009. The majority of these were previous users of other strong opioids, 168 cancer patients and 124 non-cancer patients. Pre-switch about 50% had tried one other strong opioid, while the rest had tried two or more, oxycodone was the most common pre-switch drug, used by around 50% in both groups. Following the methadone users, it was seen that in cancer patients 3 out of 4 patients received more than one prescription of methadone and that about half were still alive 12 months after the switch. Also it was seen that 44% used only methadone after the switch and no other strong opioid. Among non-cancer users, 91% used more than one prescription, and 47% used only methadone after the switch.

Finally some studies using NorPD are descriptive and do not follow users over time. One study has studied the total use from 2004-2007 and reports an increased use of opioids [55]. The yearly prevalence of users increased by 6% from 2004 to 2007 and was 9.94%. The increase in number of prescriptions dispensed was 10% in the same time period. Another study has looked at how opioids are used in children and adolescents[87] and one study has studied inappropriate use of opioids, benzodiazepines and the hypnotics zolpidem and zopiclone in elderly aged 70-89 years and has created an medicine usage index [94]. This index takes into consideration thee number of prescribers, the number of different drugs and group of drugs as well as the amounts prescribed. The index has scores from 0-20 and different cut-off points were evaluated. About 5% of the elderly population were at the second highest cut-off point and 1% at the highest cut-off. These types of studies using the whole population accurately describes the drug consumption, and as the NorPD becomes older will give more interesting results on changing trends in prescribing and can identify potential problems.

1.5.3 Linkage studies

The NorPD does not have any information about the patient other than age, gender, date of death and place of residence. Linking the NorPD to other administrative and health registries as well as health surveys allows for a whole range of other issues to be dealt with. So far the NorPD has been used in studies of the use of benzodiazepine- and benzodiazepine and alcohol use associated with opioid-use [81,85]. Whether nicotine/smoking use predicts later use of opioids[86,91]. The use of opioids and benzodiazepines before, during and after pregnancy[90] and if there is an association between parents country of birth and children's use of prescribed analgesics[92].

Persons aged 40, 45 and 60 years who where part of population based surveys in three counties in Norway, (Oslo, Oppland and Hedmark) and who self-reported no use of opioids the last 4 weeks in 2000-2001 were studied to determine whether persons who reported recent use of benzodiazepines in 2000-2001 were more likely to have had more than 12 prescriptions dispensed for opioids

in 2004-2007[85]. Adjusting for age, sex, marital status, alcohol consumption, smoking, physical activity, disability pension, cardiovascular disease and musculoskeletal symptoms, the odds ratio for using opioids when reporting previous benzodiazepine was 3.1 with a 95% confidence interval of 2.1-4.6. For a small sub sample there was additional information about chronic pain, and it was shown that while chronic pain in 2000-2001 increased the odds of using opioids in 2004-2007, benzodiazepine use in 2000-2001 still carried a significant extra effect, even stronger than chronic pain itself. This is a good example of the additional variables a linkage study can add to studies of drug consumption. The study also used data recorded before opioid use and allows for a clearer picture of what drug use came first. However, the very wide definition of at least 12 prescriptions over 4 years might be too low to draw conclusions about opioid use that might be problematic. In addition the way of defining no-opioid use in 2000-2001 (no use last 4 weeks) might introduce bias. However the study certainly indicates that benzodiazepine use carries a significant increased risk of later opioid use, independently of chronic pain or other relevant factors. In another linkage study by the same research group the association between benzodiazepines and subsequent opioid use were not seen in teetotallers but only in persons drinking alcohol [81].

A similar study was conducted by the same researchers checking whether reported nicotine use in 2000-2001 in non-opioid users were associated with the same opioid outcome of 12 or more prescriptions in 2004-2007 [86]. The odds ratio for receiving opioids with previous daily use of 10 or more cigarettes was 3.1 compared to persons with no history of smoking. This was adjusted for the same type of a wide variety of possible confounders as in the benzodiazepine study. And the association persisted independently of whether the persons reported chronic pain. Another study using the Norwegian youth health survey studied the association between smoking in 2000-2003 with having had 4 or more prescriptions dispensed for opioids during the 5 year time period of 2004-2008 [91]. The odds ratio for receiving opioids was 2.2 in an adjusted model when comparing daily smoking with no history of smoking. Even if this study used an even lower threshold to be counted as an repeated opioid user, the association

mirrored the association seen in the study of an older population with a generally much higher prevalence of opioid use[86] .

A different type of linkage was used in a study of opioid use and co-medication with benzodiazepines in women before, during and after pregnancy[90]. This study linked the nationwide medical birth database, with NorPD. The study looked at opioids and benzodiazepines dispensed 3 months before, during and 3 months after pregnancy. The study population was 194 937 women and their first pregnancy in the study period of 30th of March 2004 to January 1st 2009. The study shows how the use of opioids drops during the first and second semester from 2.6% in the three months preceding the pregnancy to 1.4% and 1.0% during first and second trimester respectively. During the third trimester the use is stable and in the three months after pregnancy the use increases to 1.8%. A small proportion also co-medicated with benzodiazepines, and this proportion was higher in women who received more than one opioid prescription. This national study with close to 100% coverage gives an excellent overview of how many pregnant women receives opioids and also what opioids they use and the extent of co-medication of benzodiazepines. It gives policy makers the complete picture when discussing opioid use in pregnancy and can be used in the future to study trends over time.

The last linkage study was a study of whether parents place of birth matters for young peoples opioid use [92]. The study has used the Norwegian youth health survey (data collected in 2000-2003) and the self-reported information about parent's birth country. It has classified the information into three groups, Norwegian parents, parents from a country with a Muslim majority and other countries. The outcome was all analgesics dispensed in 2004-2007. No differences were seen in either prevalence of analgesic use, or in the total amounts dispensed to users.

Norway has a wide range of registries and health surveys. So far only a few registries have been linked in studies of opioid consumption, and the largest health survey, the HUNT trial in the county of Nord-Trøndelag has not yet been linked with opioid data from the NorPD. In the future many more studies can be

conducted to further illuminate the opioid consumption in Norway and yield information about specific issues and sub-populations.

1.6 Challenges in pharmacoepidemiological studies of opioid consumption.

1.6.1 Measuring opioid consumption

When studying the use of drugs it is important to accurately measure what each person consumes. Since most studies cannot study what the patient actually is ingesting, the use of prescription data or administrative health database data requires some thought into measuring drug consumption. One way to measure the use is to study number of dose-units (tablets, capsules, suppositories, transdermal patches) given to the patient, and with the presumption that the daily dose is fixed at a known dose per day (one tablet per day, one patch every three days etc) it is possible to study the length of the treatment. When one in addition also have the frequency of drug dispensing or prescription renewal it is possible to estimate the adherence to the drug regime. When the dose is not known, or varies over time other units of measurement are often used. Defined Daily Dose (DDD) is a unit much used especially in Europe. It was devised in the 70's and has later been adopted as the World Health Organisation (WHO) unit of drug consumption. The WHO collaborating centre for drug statistics methodology at the Norwegian Institute of Public Health maintains the DDD system [98]. The system works in tandem with the Anatomical Chemical Therapeutic Classification (ATC) system, classifying all drugs in a five level code based on their anatomical, chemical and therapeutic characteristics. All drugs in the ATC system will also have an assigned DDD for each administration form available. The DDD is set as the most common maintenance dose in adults used for the most common indication [98]. The DDD index gets updated yearly, and as long as studies state what version of the DDD system they use [99] it will be possible to compare studies from different countries and conducted at different times.

For opioids both these approaches have their own challenges. Dosing regimen for each patient will often not be known. In the Norwegian Prescription Database the dose is only available as a string of text, and so far it is not possible to utilise

this. A further limitation to studies based on the dosing text is that prescribers frequently prescribe opioids to be used “as needed”, “as previously prescribed” or “as agreed with the physician”. Individual opioid daily dose or number of dose-units used per day will vary between patients according to the type of pain, and might also not be constant over time for the same patient. The first approach is therefore quite difficult to use. Some studies in the US estimate the days of supply for each prescription, but it is not clear if they have access to actual prescribed daily dose or if they are making estimates based on an average dose in the same way as DDD [58,100]. Using the DDD will allow studies to use the most common dose for maintenance therapy. However, when patients switch opioids, or when looking at opioids as a class, the DDD will not accurately represent the actual analgesic potency of the drug. Especially this is true when switching between weak and strong opioids, or when reporting both types of opioids together.

1.6.2 Measuring the persistence of opioid treatment.

Effective drug therapy requires drugs to be used in the correct doses and often for long enough time. For opioids long-term use also carries it’s own risks of tolerance, addiction, and problematic opioid use as well as hormonal and immunological alterations [15,18,47,48]. It is therefore often relevant to study the persistence of opioid use. When studying persistence of drug use the most common way to do this is to create treatment episodes. Treatment episodes can be created by using the date of the first prescription dispensed and calculating the duration each supply lasts allowing a certain gap before the next prescription is dispensed. If two prescriptions are filled in a shorter time interval than the estimated duration of the dispensed quantity, the extra amount can either be removed from further analysis or it can be carried forward as shown in figure 3.

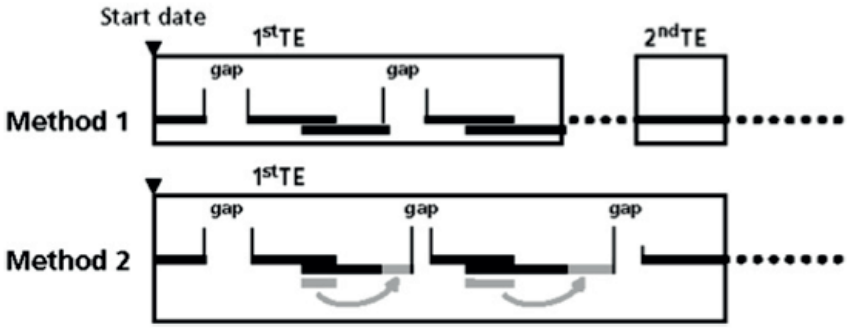

Figure 3 Different methods of creating treatment episodes. Method 1: no drugs carried over from previous prescription. Method 2: Carrying over drugs from previous prescription. (reproduced from Gardarsdottier et al. [101] with permission)

For opioids there are two challenges in establishing treatment episodes. Firstly as mentioned in chapter 1.3.2 the dose of opioids are not very standardised and might change over time. Secondly since pain might be intermittent, the acceptable gap period would also be challenging to define. Without knowledge of the exact dosing instructions, using treatment episodes will anyway be impossible. Previous studies of opioid consumption have used treatment intensity in a given time period as a measure of persistence or rather implicitly stated that very large drug amounts must mean that opioid must have been used during the whole period in question. A relevant example is a Norwegian study using 730 DDD/year as a treatment intensity that indicates that the user has used codeine persistently [82] and a different study defining likely persistent use as more than 365 DDD/year[93] . However, in general this approach is quite unsatisfactory as the use can have been unevenly distributed over the time period, and using a fixed time period will make it impossible for incident prevalent users to be counted as prevalent if they start opioids late in the fixed time period. These previous methods have had to set cut-off points high in order to gain high specificity, but they will also exclude many persistent users and thereby have lower sensitivity. As seen, it is impossible to determine persistence with certainty in opioid users, also because opioid treatment should only be used for as long as pain persists. Alternative approaches are therefore needed.

2. Research Questions

The Project has dealt with methodological challenges in studies of opioid consumption using prescription databases. Firstly the use of Defined Daily Dose as the unit of measurement of amounts in studies of opioid consumption and secondly the lack of any well described definition of persistent opioid use to apply in studies using prescription registries. Finally the persistent opioid use definitions have been applied in a study of the associations between socioeconomic variables and persistent opioid use. The research questions can be described more closely as follows:

I. Can the use of Oral Morphine Equivalents as the unit of measurement in pharmacoepidemiology studies of opioid consumption lead to different conclusions compared to using Defined Daily Doses as the unit of measurement? (Paper I)

II. How can persistent opioid use be defined in a prescription database and what is the prevalence of this use in Norway? (Paper I & II)

III. What are the socioeconomic characteristics of Norwegian persistent opioid users and how do they differ from short-term opioid users? (Paper III, using methods from paper I & II)

3. Material and Methods

3.1 Data sources

Data sources used in the project were from the Norwegian Prescription database (NorPD) and the Population and Housing Census. In addition linked to the NorPD data are data on date of death from the Central Population Register (CPR). The three data sources are described below.

3.1.1 Norwegian Prescription Database (NorPD)

The NorPD contains data on all prescriptions dispensed through pharmacies in Norway from January 1st 2004 and onwards [102–104]. All pharmacies transfer information about their dispensed prescriptions monthly to the Norwegian Institute of Public Health. The information becomes pseudonymised replacing the personal identification number (PIN), assigned to all persons living in Norway [105], with a new unique number. Information contained in the NorPD includes information about the patients' gender, birth year and place of residence[102,103]. It contains information about the drug dispensed, name, the assigned Anatomical Therapeutic Chemical (ATC) system code, and amount measured as DDD and number of dose units (such as tablets and capsules). Also included in the NorPD is the price of the drug, reimbursement status and from 2008 the diagnostic code the drug is reimbursed for. The reimbursement system in Norway allows for both ICD-10 and ICPC-2 codes to be used.

In addition to information about the patient and the drug dispensed, the NorPD also has information about the prescriber, including gender, birth year and medical speciality. The dispensing pharmacy is also registered including information about the municipality it is in (table 2). The NorPD also has information about the label containing the dosing information pharmacies put on each pack of drug. However there has been no work done to convert the dosing text into usable variables for research at present.

Table 2: Relevant variables in the NorPD to use in studies of opioid dispensing.

Pharmacy	Prescriber	Patient	Prescription
ID number	ID number	ID number	Dispensing ID
Municipality	Gender	Gender	Date of dispensing
	Year of birth	Year of birth	Product ID
	Profession	Month of death	Name of product
	”Speciality”	Year of death	Pack size
		Place of residence (municipality)	Unit of measurement for the drug
			Total DDD for ordination
			Reimbursement code
			(ICD-10 & ICPC-2)
			Total price
			Co-payment price
			Dosing instructions

3.1.2 Population and Housing Census

The data were collected in 2001 by Statistics Norway. All persons, including foreign citizens, residing in Norway at 3rd of November 2001 (according to the central population registry) were included in the census. The Census in addition to collected questionnaire data also contains data from multiple administrative databases [106]. Paper III used socioeconomic data from these administrative databases. Variables included were highest completed education, work status, marital status, immigrant background, and income.

3.1.3 Central Population Registry (CPR)

The Norwegian Tax Administration owns the registry, and Statistics Norway maintains the register for research purposes. Included in the register is data on all individuals with a PIN number [107]. All persons residing in Norway legally receive a PIN number. The register is continuously updated and Statistics Norway can link data from CPR to the NorPD by using the encrypted PIN

number. In the present project date of death was used to censor individuals followed over time in paper II.

Aggregated data on number of persons living in Norway was retrieved from the Statistics Norway website [108] and used to estimate prevalence in paper II

3.2 Methods and Study design

Paper I uses a combination of already published data and cross sectional data from the NorPD. Paper II uses 4 years of NorPD data in a prospective cohort study in order to study whether persistent opioid users remain persistent users over time. Paper III uses data from collected from two different time points, linking the cross sectional census data from 2001 with the cross sectional NorPD data from 2005 retrospectively studying socioeconomic data from 2001 in opioid users in 2005.

3.2.1 Research Question I: Comparison of OMEQ and DDD

The materials for paper I were drawn from a previously published study of opioid consumption in different European countries (Hamunen et al.[64]) as well as data from the Norwegian Prescription Database (NorPD) and a clinical study of opioid switching (Klepstad et al. [109]).

A literature search was conducted in cooperation with a co-worker in order to tabulate equianalgesic ratios for all opioids used in Norway. With sources found in this search equianalgesic ratios were estimated [26,110–119]. DDD could then be recalculated to milligram of Oral Morphine Equivalents (OMEQ) using the mg per DDD for the opioid in question (x) and its equianalgesic ratio as shown below:

$$Ratio = \frac{mg/DDD(x) \times ratio(x)}{DDD(morphine)} \times mg/DDD(x)$$

Using data published by Hamunen et al. [64] the opioid consumption for Norway, Denmark, Sweden and Finland was recalculated into OMEQ. Also the total consumption of opioids split into the different opioids in Norway in 2005 and 2008 was recalculated and the total increase calculated as DDD and as OMEQ. Finally the result of an opioid switch in a clinical study was computed as DDD and OMEQ.

3.2.2 Research Question II: Persistent opioid use

Data were extracted from the NorPD. All prescriptions of opioids dispensed in pharmacies from 2005 to 2008 were used in the study.

Three overlapping definitions of persistent opioid use were created. Since different patterns of opioid use can be considered as persistent use, three definitions were created and fitted to a different level of persistence. The strictest definition used three dimensions of persistence to identify persons with a use corresponding to daily opioid use with several doses per day or continuous serum concentration in therapeutic range. The three dimensions are Intensity, Frequency and Distribution. Intensity threshold was set as having had more than 730 DDD or 18000 mg OMEQ dispensed from, and including, the first prescription dispensed in a calendar year and in the following 365 days. Frequency was the number of prescriptions dispensed in the same 365 days, and the threshold was 10 or higher. Distribution was determined as the number of quarters of the 365 day period when opioids were dispensed, and in order to be defined as persistent opioid user all four quarters had to have at least one prescription dispensed. For the intermediate definition corresponding to at least daily use only intensity and distribution were used to define the population, the thresholds were 365 DDD or 9000 mg OMEQ in the 365 day period after first opioid dispensed and opioids dispensed in all four quarters of the period. Finally for the widest definition the thresholds were 180 DDD or 4500 mg OMEQ in 365 days and at least 3 quarters of the 365-day period. This definition fits a typical user using opioids intermittently for at least half the days of a year.

Applying these definitions to opioid users in 2005, the definitions captured the persistent opioid use 31. December 2005 and these users were followed for two more years, for a total follow up of 1095 days from the first prescription. The status was measured at the end of both 2006 and 2007 and the percentage of persistent users who where in the same definition each year as well as in any

persistent opioid use definition were calculated. In order to be considered at risk for being persistent opioid user, the person had to be alive at the measuring points.

Also in order to test whether the definitions capture true long-term use an analysis method called waiting-time distribution (WTD) was applied (Only in thesis, not in paper II). WTD is a graphical approach to analyses of prevalence, incidence and prevalence/incidence rate relations [120]. Using the concept first developed by Hallas et al. [121] and a parametric method developed by Støvring [122] it is possible to calculate the prevalence and incidence, and estimate the average length of treatment.

WTD can be explained as a graph showing the frequency of time until the first prescription is dispensed after a given start date. Prevalent users will have a short waiting time, while after a time the graph will be dominated by incident users. It is then possible to visually determine the incidence rate and with the help of Stata to get parametric estimates of the number of incident users and the number of prevalent users. The rate between prevalent users and incident users will be an estimate of average treatment length [120,123]

In order to test the three different definitions of persistent opioid use further than the scope of an article allowed, the waiting-time distribution analysis was done for four groups; all opioid users, and users recognised by each of the three definitions of persistent opioid use. The data used were data from 2005-2006. This means that the population in this analysis is identical to the study population of paper II.

3.2.3 Research Question III: Socioeconomy of persistent opioid users

From the national population and housing census in 2001 data on socioeconomy were linked to NorPD data from 2005-2006.

Persons had to have complete socioeconomic data in order to be part of the study population. In addition all persons younger than 35 were excluded in order to ensure that the variable "highest finished education" would reflect the final education for most persons.

The population fitting these criteria was 2'369'564 individuals. Of these 329'125 persons had at least one prescription of an opioid dispensed in 2005.

After excluding anyone with at least one prescription dispensed for palliation (23'314 individuals), the opioid using population was divided into persistent opioid users (N: 15'113), (defined as receiving at least 365 DDD or 18000 mg OMEQ in the 365 days following the first opioid dispensed, and with opioids dispensed in all four quarters of the year following the first prescription) and short-term opioid users with three or fewer prescriptions dispensed in 2005 (N: 214'061). 76'637 individuals did not fit either group and were excluded.

The socioeconomic variables used in the study are described below; in addition the categories of each variable are shown in parenthesis. Socioeconomic variables: income, (quartiles), education, (lower secondary school, upper secondary school, 3 years of college, 4+ years of college) Immigrant status (person or parents are immigrants, or no immigrant background), work status, (working, not-working, disability pension) and marital status (single, married, divorced/separated, widow/widower).

Income was reported as household income and was scaled by dividing the income with the square root of the household size as the personal income variable. This scale is widely used amongst others by the organisation for economic cooperation and development, OECD [124].

The analyses conducted were logistic regression analyses stratified on gender and age above/below 67 years old. In the models for persons aged 35-66, work-status was included, in persons 67 and older, it was excluded due to the general retirement age being 67 years.

The modifying effect of work status was also studied by seeing how the effect of the other variables changed when stratifying for work status. These were exploratory analyses and no statistical testing was conducted.

In the thesis additional analyses to see whether there were any differences in the prevalence of persistent opioid use in different counties in Norway were conducted. The county of residence was extracted from a NorPD variable containing the ISO 3166-2 [125] code for which municipality the patients live in. Prevalence of persistent opioid use was determined at 31. December 2007, using NorPD data. All three definitions were used. All opioid users were included, both users of opioids for malignant (palliation) and non-malignant pain. The data were then aggregated to county level and transferred to the map program Magic Maps [126].

3.3 Programming code for automation

In order to be able to reproduce the results and also transfer the methods to other studies it has been necessary to create general programming code for different essential steps in the data management. Three steps are especially critical or special; the conversion from DDD to oral morphine equivalents, the identification of persons meeting the criteria of the different definitions of persistent opioid use, and the more specific code for creating the custom-made figure 2 in paper III. This figure has no ready-made commands in Stata and the results from the logistic regressions had to be extracted and transferred into drawing each line of the figure. The exact programming code can be studied with commentaries in the appendix.

3.3.1 OMEQ

In order to create mg oral morphine equivalents for each prescription it is necessary to use the number of DDDs for each prescription and combine this with the actual dose per DDD and the equianalgesic ratio. However, the challenge was in the fact that each opioid formulation has its own DDD dose and equianalgesic ratio. In order to calculate the OMEQ dose it is therefore necessary to use the product ID, unique for each different product. For all opioids with more than one DDD dose or more than one equianalgesic ratio the conversion had to go through the opioid's product ID. There are hundreds of different product ID numbers for opioids in Norway so using the automation code created will be essential to avoid large amounts of duplication of work. However the code needs to be maintained each year, by adding the new product ID numbers available on the market. If this is done the code should save a lot of work.

3.3.2 Definitions of persistent opioid use

When defining persistent opioid use the code for OMEQ is used and is combined with other variables created. The variables needed to define persistent opioid use are firstly the quarter of the year each prescription is dispensed in and secondly the number of prescriptions dispensed during 365 days following the first prescription dispensed. In addition it is necessary to define the 365 day period in which each patient's opioid use will be measured . This is performed by

using the date for the first opioid prescribed in the dataset for each patient, and for each later prescription evaluate whether it is within 365 days of this period and remove any prescriptions that are not. In order to do this it is clear that data from two calendar years are needed. Once all prescriptions dispensed more than a year after the first one is removed the data can be aggregated for each patient, the number of quarters created, the total volume of opioids dispensed in DDD and OMEQ and the number of prescriptions calculated. These variables can then be coded into the respective cut-off points for each definition and combined to determine whether each patient matches the criteria set.

3.3.3 Figure 2 in paper III

From a technical perspective this is slightly more advanced programming than the other two parts. Figure 2 is a figure where for each category of a socioeconomic variable the unadjusted odds ratio is drawn as a horizontal line, and then as vertical lines the adjusted odds ratio is drawn stratified for work status, a total of four lines for each category are drawn. These figures are made by extracting the results from the logistic regressions done for a simple unadjusted model with only one independent variable, and for the same simple model but done for the subpopulations that are working, are not working or are on disability pension. These results are then stored and are combined to draw the lines in the figure. To combine them several loops are necessary as well as creating macros extracting different parts of the regression coefficient matrix each time. The code shown in the appendix can easily be amended to work with other data by changing the "settings" defined in the first nine lines of code.

3.4 Ethics

The linkage study in paper III was endorsed by the Regional Committee for Medical Research Ethics and data linkage was approved by The Norwegian Data Inspectorate. For the other studies no special ethical permission was needed. The Research Council of Norway funded this work (project number 196213).

4. Results

4.1 Research Question I: Comparison of OMEQ and DDD

In order to answer research question I, the study reported in paper I was conducted. The objective of the study was to examine whether the use of oral morphine equivalents (OMEQ) in studies of opioid consumption will give additional insights as compared with using Defined Daily Doses (DDD) alone.

To investigate whether OMEQ had any potential to change results in studies using DDD the OMEQ/DDD ratio was calculated for each opioid formulation. If the resulting ratio was 1 the OMEQ would match the DDD of oral morphine perfectly. The results showed that for weak opioids (WHO step II) all ratios were in the range of 0.1 and 0.5, and that for some strong opioids (WHO step III) such as sublingual/transmucosal fentanyl, sublingual buprenorphine and per oral ketobemidone the ratio also differed clinically significantly from 1. No opioids except the basis for OMEQ, oral morphine, had a perfect match. (figure 4)

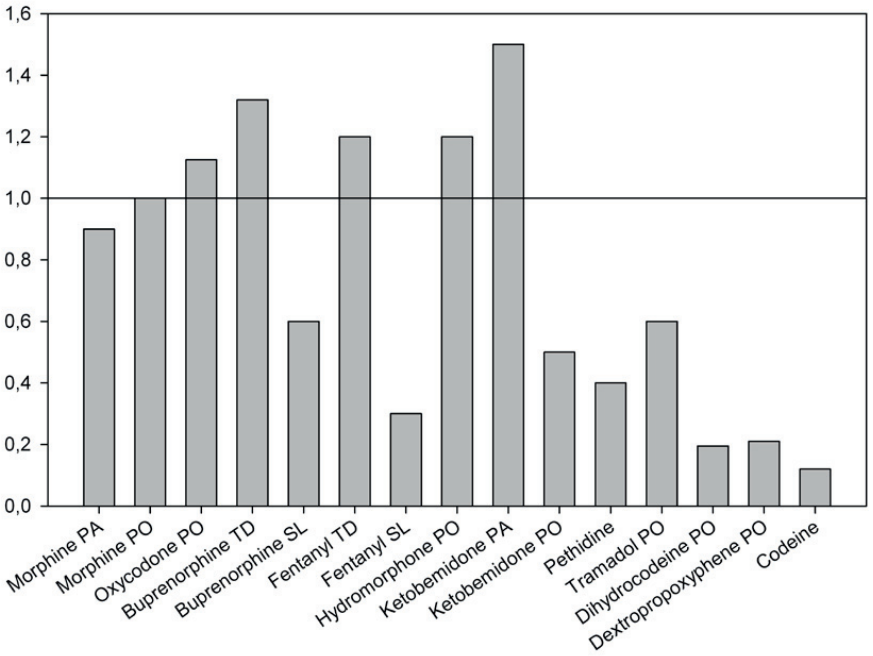

Figure 4: The relationship between DDD and OMEQ for different opioids. Perfect correspondence between DDD and OMEQ is 1. Deviation means that the OMEQ does not correspond to the DDD. Abbreviations: PO: Per Oral, TD: Transdermal, SL: Sublingual PA: Parenteral.

The equianalgesic ratios from paper I are shown below (table 3). For paper III the ratio of codeine-paracetamol was changed from 0.10 to 0.15 as this seemed to be a more clinically correct ratio [48,119].

Comparison of countries total opioid consumption:

Comparing Denmark, Sweden, Finland and Norway's total opioid consumption using DDD resulted in Sweden having the highest consumption, followed by Norway and Denmark. Using OMEQ reversed this order completely. Finland had the lowest consumption in both comparisons. This change in order persisted when using the bottom and top of the range of equianalgesic ratios in a sensitivity analysis.

Table 3: Equianalgesic ratios used in paper I

Drug	Adm.	DDD (mg)	Range	Equianalgesic ratio
Morphine	PO	100	1	1
Morphine	PA	30	-	3
Oxycodone	PO	75	1.3-2.0	1.5
Buprenorphine	TD	1.2	110	110
Buprenorphine	SL	1.2	33.3-60	50
Fentanyl	TD	1.2	68-150	100
Fentanyl	SL	0.6	50	50§
Hydromorphone	PO	20	3.6-8.0	6
Ketobemidone	PA	50	3.0	3
Ketobemidone	PO	50	1	1§
Pethidine	PO	400	0.03-0.13	0.1
Codeine	PO	90/120*	0.05-0.15	0.1
Tramadol	PO	300	0.1-0.2	0.2
Dihydrocodeine	PO	150	0.1-0.16	0.13
Dextropropoxyphene	PO	140*	0.15	0.15

PO = Per Oral, TD = Transdermal, SL Sublingual PA = Parenteral
§: calculated from bioequivalence data found in the Summary of product characteristics for these drugs (Actiq®, (Cephalon) and Ketorax ® (Pfizer).) *: The DDD for these compounds are based on combinations with paracetamol.

Opioid market share and increase in use in Norway 2004-2008:

The most used opioid using DDD was Codeine and paracetamol in combination with a share of 65% in 2008. Weak opioids in total accounted for 81.9% of the dispensed opioids. Using OMEQ tramadol accounted for 23.4% and codeine-paracetamol for 20.4%. Oxycodone accounted for 19% with morphine and fentanyl behind with 15 and 13%. The increase in dispensed opioids from 2004 to 2008 was 6.7% when using DDD, while it was 23.6% when using OMEQ.

Opioid switching study:

If the results in the clinical study had been reported as DDD the DDD/day would have decreased from 2 for codeine-paracetamol and 4 for dextropropoxyphene before the switch to 0.97 after the switch to morphine. For OMEQ the pre switch doses were 24 mg for codeine-paracetamol and 84 mg for dextropropoxyphene and it increased after the switch to 97 mg of morphine, corresponding to the reported improvement of pain control.

4.2 Research Question II: Persistent opioid use

Using the OMEQ unit of measurement investigated in paper I, research question II was studied in paper II. The study aimed at developing definitions of persistent opioid use to apply in prescription database studies.

Table 4: Definitions of persistent opioid use. Cut-off points per 365 days and typical clinical scenarios connected with each definition of persistent opioid use

	Amount of Opioid	**Number of Prescriptions**	**Number of Quarters**	**Typical Clinical Scenario**
Wide Definition	> 180 DDD *OR* > 4500 mg OMEQ.		At least three quarters	Persons use opioids at least 1/2 of the days in a year
Intermediary Definition	> 365 DDD *OR* > 9000 mg OMEQ.		All four quarters	Persons use opioids at least once daily
Strict Definition	>730 DDD *OR* > 18000 mg OMEQ.	At least 10 prescriptions	All four quarters	Persons with continuous therapeutic concentrations of opioids

At the end of the three year follow-up the retention within any of the three definitions was 83, 84 and 68% for the strict, intermediary and wide definition, respectively. This finding signifies that a large percentage of persistent opioid users in the definitions continue to use opioids persistently for at least three years.

The point prevalence of persistent opioid use in Norway (N: 4'681'134) at the end of 2007 was 0.16% for the strict definition, 0.50% for the intermediary definition and 1.08% for the wide definition. This was assessed as a reasonable separation of the different definitions.

In addition to the results published in paper II a waiting time analysis was run for all opioid users, as well as users defined as persistent opioid users by each of the three definitions of persistent use. The visual results are shown in figure 5. As seen in all opioid users the percentage of first prescriptions dispensed are high throughout the year, while the percentage is much lower in all three definitions. This is reflected in table 5 were the number of incident users are high in all opioid users compared to the total number of users, while the percentage is much lower in the persistent opioid use definitions. The average treatment duration increases from 0.42 years (22 weeks) in all opioid users to 7.5 years for the wide definition, 11.6 years in the intermediary definition and 14.2 years in the strict definition.

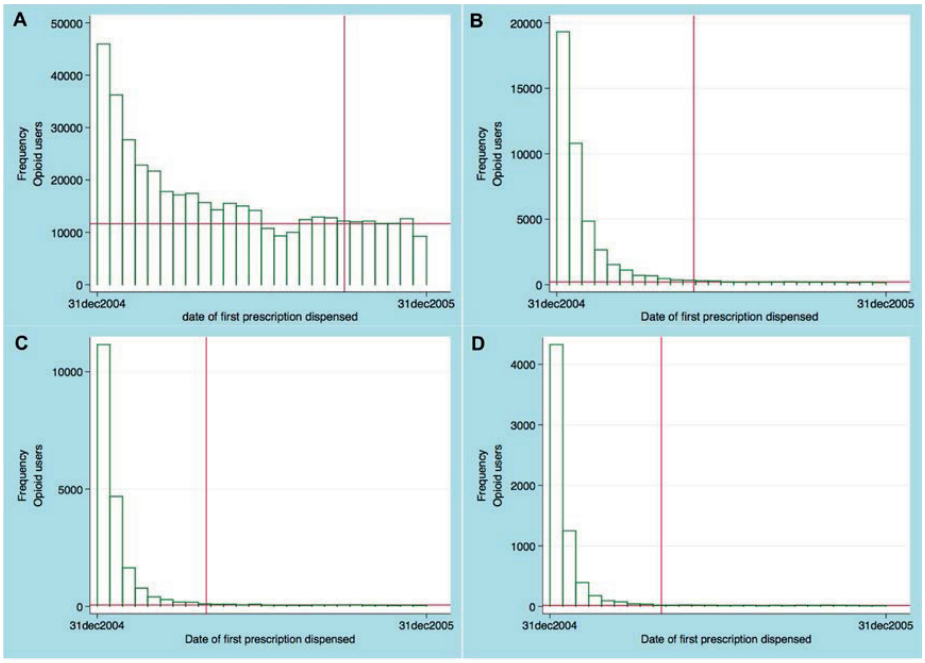

Figure 5: Waiting time distribution analysis of opioid users in Norway in 2005. A: All opioid users, B: Wide definition, C: Intermediary definition, D: Strict definition. Each bar represents two weeks; the vertical red line represents the cut-off point where all users are incident after this, and the horizontal red line represents the level of incident users estimated from the cut-off point.

Table 5 Numerical results of waiting time distribution analyses.

	All opioid users	Wide definition	Intermediary definition	Strict definition
Number of persons	432087	45910	20474	6702
Number of Incident users	303423	5393	1628	440
Number of prevalent users	128664	40517	18847	6262
Prevalence	0.30	0.88	0.92	0.93
Treatment length estimate	0.42 years	7.5 years	11.6 years	14.2 years

4.3 Research Question III: socioeconomy of persistent opioid users

Using the intermediate definition from paper II, the socioeconomic associations with persistent opioid use was studied in paper III.

In persons aged from 35 to 67 years disability pension was more common for persistent opioid users compared to short-term users (48 versus 16 percent for women, and 36 versus 9 percent for men, respectively). The adjusted odds ratios for persistent opioid use in subjects receiving disability pension were 6.5 and 5.8 for women and men, respectively. Being divorced/separated was associated with persistent opioid use, and an association between persistent opioid use and education, unemployment and income was also found. In the analyses of persons older than 67 years in 2001, the patterns were similar as in the younger aged groups. However most effects were weaker, the exception was marital status where the association was stronger in the older age group. In addition to these results reported in paper III the association between persistent opioid use and county of residence has been studied and reported below.

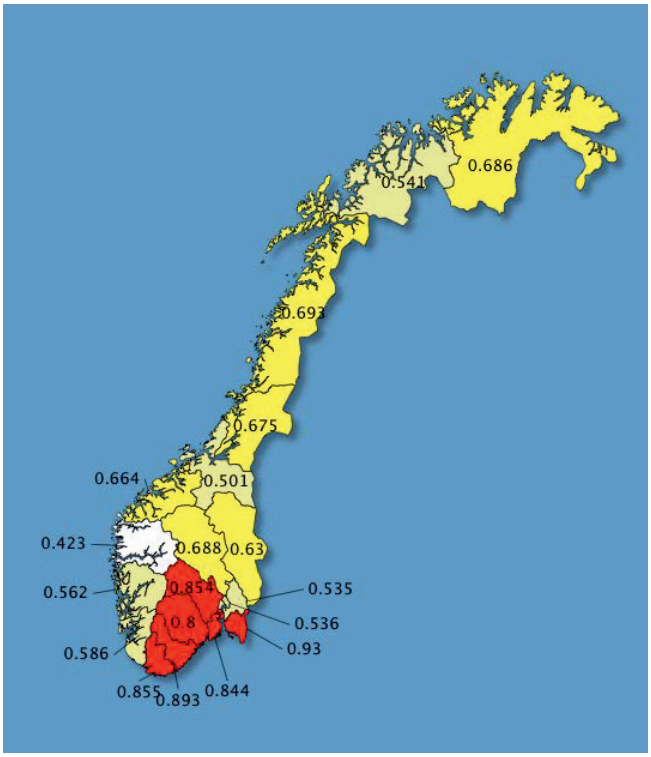

Figure 6: Prevalence of persistent opioid users in the different counties of Norway shown for the intermediary definition, red indicates high prevalence, white, low. Measured as percentage

Seen in figure 6 the county with the lowest prevalence of persistent use, Sogn og Fjordane (0.42%), has less than half of the prevalence than in the county with the highest use, Østfold (0.93%). This corresponds to an odds ratio of 2.2. In general the highest prevalence of persistent opioid use is found on the South-eastern coast of Norway, while the south west/west of Norway has a low prevalence. The same pattern is seen for all three definitions (not shown).

5. Discussion

The three papers in this thesis build upon each other, paper II would not be possible without the ground work done in paper I, and Paper III uses one of the definitions from paper II to define the study population. As such they form three distinct steps on a ladder, and the two first steps can now be implemented in other studies by other researchers.

5.1 Methodological strength and limitations of studies

The major strength of the studies in this thesis is the use of population data and the lack of any significant selection bias plaguing studies with other designs and studies based on other data sources. Another major strength is the possibility to study the prescriptions to individual patients longitudinally. The NorPD covers 100% of pharmacies in Norway meaning that every single prescription dispensed in Norway will be collected and included in the NorPD. In addition the national system of giving every individual living in Norway a personal identification number (PIN) and using the PIN when registering prescriptions allows for a more certain following of individuals' use of drugs [103]. The PIN follows a person from birth to death, and is used directly or pseudonymised in virtually all national registries. The PIN is used to conduct the linkage of socioeconomic data from the population and housing census and prescription data from the NorPD in paper III. These features of the data sources insures that the quality of data is good. Combine this high quality data with well-documented, relevant and tested methods, of measuring both opioid volume consumed, and persistent opioid use, and it is possible to conduct population studies with high internal validity.

However, there are some challenges to be aware of. Firstly the validity of both the equianalgesic ratios used and the persistent opioid use definitions, secondly the way the systems in Norway do not capture individuals use of drugs in institutions such as nursing homes, and finally the use socioeconomic study does

not measure socioeconomic factors at the same time as opioid consumption, with the possibility of persons changing status significantly in the 3-4 years between observed socioeconomic factors and measured opioid consumption.

Both the strengths and weaknesses will be discussed in more detail below.

5.1.1 Strengths of the data and the analyses

Before going into the specifics of the data sources, and the comparison with other studies, it is worth mentioning the general advantage of following individual patients over time. As described in the introduction, many studies, especially some European ones only use aggregated data from whole-sellers or other aggregated sources [63,64,66,71,74]. In addition it is an advantage to study dispensed drugs rather than prescribed [56]. Given that it is impossible to follow the actual ingestion of drugs in patients, studying the drugs actually bought by patients is the closest one can come to ingestion in a population study.

The Norwegian prescription database covers about 88% of the volume of opioids used in Norway [55]. The remaining volume is used by hospitals and institutions like nursing homes. This complete coverage is in contrast to the American studies using insurance data, both from private companies and, in elderly, from Medicare [58,60,127–131]. The size of these insurance databases range from a few hundred thousand to a few million. This means that it only covers a few percent of the American population, and only a selected population, often in a single state, that can afford these different private health insurance plans [132]. Even after adjusting age and gender for the general population these studies will always suffer the risk of selection bias and therefore an unknown external validity for the population as a whole.

Finally the way paper II has defined persistent opioid use, using both amount and distribution of use over 365 days, and defining three different levels of opioid use as persistent allows for more flexible research into persistent opioid use. Since different research questions require different levels of persistent opioid use, paper II supplies a selection of definitions.

5.1.2 Weaknesses of the data and the analyses

The major weakness of the papers in this thesis and indeed in most if not all observational studies is the clinical validity of the results. In each of the papers there is a different issue with validity.

For paper I the validity of the equianalgesic ratios will always hunt studies like these. There is no consensus of what doses are equianalgesic and there are many different equianalgesic tables[26,66,113]. Even when they are based on clinical evidence, the majority of studies of opioid rotation and switching are done in short-term users where tolerance has not developed. This has led to different pharmacoepidemiological studies using different equianalgesic tables and this does not only lead to questions about validity but also leads to difficulties in evaluating and comparing different studies. In contrast to this is the DDD system. It allows for comparisons between studies, and also over studies from different years. The use of OMEQ is necessary to get a better picture of individuals' opioid use, but often the use of DDD in addition will give information that can be more easily compared especially with other Norwegian and European studies.

In paper II the clinical validity of the definitions of persistent opioid use can not be determined using the data sources available in this thesis. The three clinical scenarios will not fit all persons identified by the definitions, and the prevalence results using the definitions should not be used as the exact real number of persistent users but rather as an estimate. Some American studies [58,100] use days of supply per prescription to create more exact episodes of opioid use. This approach would be better if it was possible to determine this with any certainty for opioid prescriptions. One of the American studies uses maximum daily dose as the days of supply and this is not a good way of determining it [58]. For other studies it is impossible to extract the method behind the calculation of supply [100]. In Norway it would be possible to find days of supply if the dosing text was analysed, but text mining is complex and have not yet been done on any drugs in Norway. An unknown proportion of prescriptions of opioids will also not have dosing instructions other than "use as prescribed" or "use when needed". The existing definitions can also be used in samples with more clinical data, for

instance the Health Survey of Nord-Trøndelag, and in the future this will be done as part of another ph.d. project started.

In paper III there is an additional issue related to the socioeconomic variables used in the study. Firstly since there is a four-year period between measuring socioeconomy and persistent opioid use some variables might change significantly during these four years. This is especially true for work-status, marital-status and income. Secondly the choice of using household income divided by the square-root of number of persons in the household might be questioned. The methodology has been used extensively in income statistics from OECD but other equivalence scales exist to create an income variable (OECD). There seems to be no preference to what scale is the best, so the choice in paper III is arbitrary made on the basis that it seems like a sensible scaling of income. Furthermore the work-status variable only measures income from employment/self-employment, no income or disability pension. The no income group will be very diverse and will include housewives, persons actively searching for work and people not actively searching for work. In general it is important to remember that the external validity of a study such as the one in paper III will be limited. Other countries with any differences such as a different health care system, different criteria for disability pension, different mix of immigrants, different educational system, different tax rules for cohabitating and generally different economical and cultural background might produce other results than the ones observed in this study. Paper III merely establishes the associations between persistent opioid use and socioeconomy in Norway.

Finally the studies conducted in this thesis are not able to get into the root causes of opioid use. For each patient using opioids there is a diagnosis behind the opioid use. It might be a broken arm, a painful dental extraction or chronic conditions such as neuropathy or lower back pain. There might be co-morbidities making the patient more likely to use opioids persistently and maybe problematically such as a variety of psychiatric diagnosis or previous history of drug abuse. In order to really say what our findings mean for the individuals using opioids and for public health, data on diagnosis and other clinical data are needed. There are now data available in Norway both from

national health surveys and from the new patient registry [133] and in the future such data sources should be used to further investigate who receives opioids inappropriately and which non-opioid using patients that are in pain and that could benefit from receiving opioids.

5.2 Discussion of findings

5.2.1 Research Question I: Comparison of OMEQ and DDD

In studies of opioid consumption both DDD and morphine equivalents of different kinds have been used. The ATC/DDD system is better known in Europe so studies using DDD are all European [63–65,71,74]. This includes all previous studies of opioid consumption using the NorPD in Norway [55,82,87,88,93]. In the US studies mostly use some kind of recalculation of doses to morphine equivalents [58,60,100]. Danish studies use both DDD and oral morphine equivalents [66–70]. Also in international statistics both units of measurement are in use. The INCB [53] uses kg of each opioid for country-wise opioid statistics, but now also reports a simplified DDD/million inhabitants/day. The PPSG group [54] in the US uses the INCB data for their statistics but converts them to morphine equivalents. However a main question has not been addressed previously: what is the difference in results when using one or the other unit of measurement? Paper I addresses this question by comparing the two units of measurement in three different situations.

As the results show, there is a significant difference between using DDD and OMEQ. The magnitude and direction of the difference is not easy to predict. For weak opioids such as codeine, dextropropoxyphene and tramadol, as well as certain administration forms of strong opioids such as transdermal fentanyl the defined daily dose is set lower than would be expected based on the potency of the substances. When using DDD, these drugs and formulations will thus be weighted heavier than other opioids such as morphine and oxycodone. This is the reason why the increase in opioid consumption in Norway was lower using DDD than OMEQ, as the use of the predominant opioid is stable. Because the prescription level of codeine-paracetamol combinations is high and stable, this

camouflages the increase of stronger opioids. The same is true for the comparison of different countries. Countries with a high consumption of weak opioids such as Norway and Sweden will get a higher total consumption than countries using more strong opioids such as Denmark.

In conclusion the study has clearly shown that results can differ significantly using an equianalgesic unit of measurement (OMEQ) compared to using the WHO methodology of defined daily doses (DDD). This is the first time a study has compared these two methods and paper I can provide guidance for other researchers when selecting which unit of measurement to use in studies of opioid use.

5.2.2 Research Question II: Persistent opioid use

As shown in the introduction, chronic pain has several different definitions: 3 months, 6 months as well as a combination of duration and minimum pain intensity. Several studies of opioid use have emulated the chronic pain definitions and used similar definitions or even shorter periods [58,134]. However, when considering the risks of addiction and other problems with opioid use, as well as other potentially addictive drugs such as benzodiazepines, the longer a patient uses the drug the more relevant these problems and their underlying medical condition become. Paper II studies the use of opioid for at least 365 days, and has used amount of opioid as well as distribution of use and frequency of dispensing for the strictest definition. Persistent opioid use was chosen as the term rather than chronic opioid use, both because persistence is a well known expression from pharmacoepidemiological studies of other drugs [135–137] and to avoid the implied connection with the definitions of chronic pain. Persistent opioid use in Norway was between 0.16 and 1.07% using the definitions. This seems reasonable compared to previous findings from the NorPD. About 0.8% of the Norwegian population use more than 120 DDD of codeine-paracetamol in a calendar year and 0.04% use more than 730 DDD [80,82]. When following the study population for two additional years a high percentage of persons identified as

persistent opioid users continued to use opioids persistently. This indicates that the definitions capture true long-term persistence. Since treatment with opioids generally is not meant to be life long it is not known what the optimal percentage of 3 years persistence would have been for the definitions.

The prevalence of persistent opioid use in Norway seems to be lower than one could expect after reading studies from countries such as the US and Denmark as well as the Norwegian results from the Breivik phone survey [14,20,22,58]. The 1.07% of the Norwegian population in the widest definition has a fairly low cut-off point for the amounts of opioids use, and during a 365-day period they can have no opioids dispensed in a 90-day period. Paper II is the first study from the NorPD looking at such low levels of persistent opioid use, and the reported prevalence can be seen as an estimate for the maximum extent of use that is, or can become, problematic.

The analysis of waiting time distribution complements the retention analyses of paper II, but was not included in the paper since it was deemed to theoretical to fit with the clinical focus of the article. The results of the waiting time distribution analyses show that there is a clear difference between all opioid users and the persistent opioid users. It estimates the incidence of persistent opioid use, as this was not done in paper II, and it also provides an estimate of treatment length, or actually an estimate of the average time persons stay persistent opioid users. The estimated incidence of persistent opioid use was low, only about 12% of the users for the widest definition falling for the two others down to 7-8% for the strict definition. For all non-persistent users it is already known that 71% did not receive any opioids in the previous year (paper II), and this is similar to the estimated incidence of the waiting time distribution (70%). The estimated length of persistent opioid use was high. It has to be understood that this is an estimate of the average length a persistent user of opioid will use opioids persistently at the time of measurement. Changing incidence and prevalence could change this estimate. So rather than being taken literally, the size of the estimates should be seen and can be used to compare trends over time. If many more start using opioids persistently, the estimate will decrease, whereas if the incidence decreases, the estimate will increase.

5.2.3 Research Question III: Socioeconomy of persistent opioid users

Previous international studies have shown association between different socioeconomic factors and pain or opioid use. A study of opioid use for more than 4 weeks, more than 4 days per week showed a strong association with opioid use and low education [134]. A different study of persons with chronic pain showed that persons with completed high school and some college education were more likely to use opioids, and that higher income was associated with more opioid use [129]. The exceptions were persons with college degrees and persons with more than 70000 dollars per year in income. In contrast to this finding a different study found that education and higher income both were associated with less chronic pain and less opioid use in chronic pain patients [20]. The study also reported that living alone was associated with both higher prevalence of chronic pain and in these chronic pain patients more opioids were used. Finally it has been shown that in patients with chronic pain, there is an association between chronic work loss and opioid use, especially when strong opioids are used for more than 90 days [127]. However, the impact of socioeconomy will also depend on the society as a whole. Norway is quite different from the US and other industrialised countries in many regards such as universal health-care, unemployment and employment rates [138] and background of immigrants therefore results from foreign studies might have limited applicability in Norway. In Norway a study has characterised persons in chronic pain using a questionnaire [13]. In this study a multiple logistic regression analysis was done and it was seen that persons in chronic pain were more likely to have less education, that employment status in it self had no effect and that marital status did not matter. This is in contrast to the findings in paper III showing an association between persistent opioid use and these factors. This seems to indicate that high socioeconomic "status" is not related to less pain, but that this pain is treated and dealt with differently with less persistent opioid use.

In paper III the socioeconomic factors studies were: Income, education, marital status, immigrant background. The analyses were conducted stratified on gender and age. The age strata were 35-67 years and 68 years and older. The stratified populations are all large and therefore small differences in odds ratio will be statistically significant. The smallest differences statistically significant (99% confidence interval) in the largest group (women 35-67 years old) were odds ratios of 0.88 and 0.89 and for the smallest group (men, 68 years and older) odds ratios of 1.14 and 0.78 were statistically significant. The size of the association therefore has to be interpreted in what is clinically significant. The strongest association was found between work status and persistent opioid use. This is not unsurprising as painful conditions can lead to both persistent opioid use and inability to work. Without a prospective study design it is impossible to study whether non-working/disability pension came first and opioid use followed or the opposite, and whether opioid doses increase or decrease when persons no longer work. Another association seen in both genders and both age groups is the association between being divorced/separated and persistent opioid use. Previous studies of socioeconomy and drug use have tended to group all persons living alone, and paper III indicates that this should be avoided [20,139,140] Single individuals and widows/widowers show no association with persistent opioid use, and mixing these in with divorcees would lessen the association seen.

The analysis of county-wise differences of persistent opioid use points to the fact that there is something with either individuals or prescribers in certain areas of Norway that gives rise to this large difference in prevalence. It is already well known that the total drug consumption is different in different counties [141] as well as the total opioid consumption [142]. However, the difference seen in the prevalence of persistent opioid use is much larger than the differences in total drug and opioid consumption. This indicates that there are additional mechanisms at play in addition to the generally lower drug consumption in some counties. The difference between the county with the lowest and highest prevalence of persistent opioid use, using the intermediary definition, is over 120%. Further analysis of differences between counties both in terms of socioeconomy and factors such as distance to the nearest doctor and pharmacy

is needed. A study from 1978 [143] using whole-sale data and aggregated socioeconomic variables to explain the county difference in total drug consumption can shed some light into which variables that can be relevant, but with more individual data available better and more revealing analysis is possible.

6. Conclusions

Research question I: Can the use of Oral Morphine Equivalents as the unit of measurement in pharmacoepidemiology studies of opioid consumption lead to different conclusions compared to using Defined Daily Doses as the unit of measurement?

In paper I the first research question was answered. There is a significant discrepancy between the DDD doses for each opioid and the equianalgesic ratios. Weak opioids have a higher DDD than the equianalgesic ratio would suggest. For some strong opioids, especially transdermal formulations of fentanyl and buprenorphine, the same discrepancy is also quite pronounced. These differences can, as paper I showed, give rise to different conclusions when OMEQ is used in addition to DDD.

Research Question II: How can persistent opioid use be defined in a prescription database and what is the prevalence of this use in Norway?

Paper II defined persistent opioid taking into account the amount of opioids measured as DDD and OMEQ dispensed during a 365-day period. The definitions had a high degree of retention following patients for a total of three years and the Norwegian point prevalence of persistent opioid use at 31. December 2007 was 0.16%, 0.50% and 1.07% for the strict, intermediate and wide definition respectively.

Research question III: What are the socioeconomic characteristics of Norwegian persistent opioid users and how to they differ from short-term opioid users?

The third question, studying the socioeconomic features of persistent opioid users, was answered in paper III. It was found that persistent opioid users compared with short-term opioid users in Norway were more likely to have lower education, lower income, be unemployed or on disability pension, have

ethnically Norwegian parents and be divorced or separated. For persistent opioid users older than 67, the same associations were seen but were weaker except the association with ethnic background that disappeared and the association with marital status that was stronger.

7. Issues for future research.

This thesis has dealt with a couple of essential challenges in pharmacoepidemiological studies of opioid consumption as described by research question I and II. Both challenges were well recognized, but the literature does not include data on the impact of the choices made to resolve the challenges. Neither had any methodological testing been performed.

With the papers in this thesis the difference between using DDD and equianalgesic doses have been clearly shown for the first time. In addition the use of OMEQ in defining persistent opioid use in paper II allows for single definitions to encompass both users of weak opioids, users of strong opioids, as well as users who switch between these two groups, and it is robust no matter which opioid is used. This allowed a clear comparison between long-term persistent opioid users and short-term users and the socioeconomic variables associated with persistent opioid use in paper III. With the knowledge of what the prevalence of persistent opioid use is in Norway more informed guidelines can be developed. As an example it is now known that more than half the persistent opioid users in Norway use opioids in fairly low doses and/or not every day. This should mean that this group should receive more attention in future guidelines of opioid use. The results also inform clinicians that only a small proportion of opioid users use opioids frequently and/or in high doses and will be at risk for developing problematic opioid use.

In the future the focus should be on conducting more linkage studies using both the NorPD and other administrative databases, and also health surveys. This would give more information about the patients that are being studied. Especially health surveys could give more information about co-morbidities, life style, quality of life and pain conditions. This would be essential in order to infer something on whether the use of opioids in Norway is appropriate or not. The work included in this thesis has built a foundation for conduction of linkage studies targeting persistent opioid users. Such future studies will be able to investigate whether all persistent opioid users are CNMP patients, and the prevalence of persistent opioid use in CNMP patients in Norway.

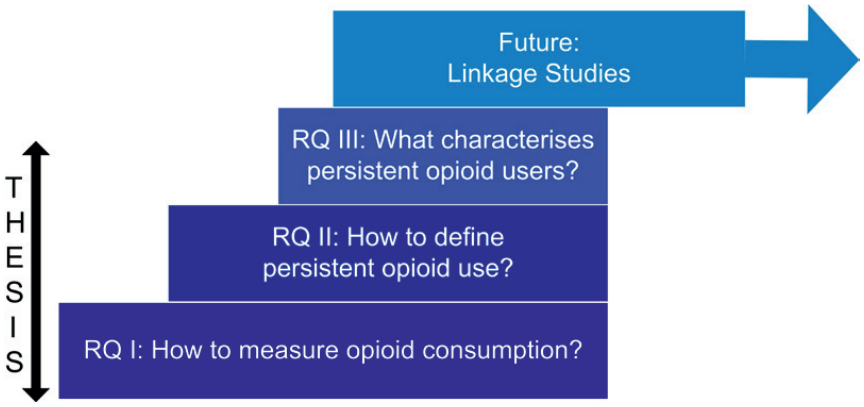

Figure 7: future research building on the work in this thesis

Another important development would be to try to get more longitudinal study designs, in order to study how patients' opioid use change over time as their pain and other factors change. One way would be to do a study using the longitudinal data from the Pain-HUNT survey. In this study 3548 patients have now completed 3 years. The study consists of questionnaires being sent out every three months for the first year, and then yearly for the next three years. Around 30% have reported chronic pain [9]. Whether a study like this would have statistical strength to give solid conclusions is unclear, but the Pain-HUNT is still a unique source of longitudinal pain data from a population sample.

One issue in the NorPD is how dosing information is collected but not used. In the future work should be put into developing a method for quantifying the dosing instructions and using this data to determine what doses opioid users are being prescribed and this would also potentially allow the creation of treatment episodes. However, it still remains to see how many dispensed prescriptions for opioids that actually contain a useful dosing instruction to the patient.

Finally one issue with the Norwegian opioid consumption has so far not been studied. The differences in persistent opioid consumption between geographical areas in Norway are shown to be significant in this thesis. The reasons for this would be interesting to know more about. Is this just related to the differences in prevalence of pain, or are there other factors also influencing these differences?

8. References

1. Meldrum ML ed. *Opioids and Pain Relief: A Historical Perspective*. 1st ed. Seattle: IASP Press; 2003.

2. Rey R. *The History of Pain*. Harvard University Press; 1995.

3. Fishman SM, Ballantyne JC, Rathmell JP eds. Intellectual Milestones in our Understanding and Treatment of Pain. In: *Bonica's Management of Pain.* 4th ed. Lippincott Williams & Wilkins; 2009:1-13.

4. Melzack R, Wall PD. Pain mechanisms: a new theory. *Science*. 1965;150(699):971-9.

5. Besson J. The neurobiology of pain. *Lancet*. 1999;353(9164):1610–1615.

6. Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. *Science*. 2000;288(5472):1765-9.

7. Fishman SM, Ballantyne JC, Rathmell JP eds. Pain Terms and Taxonomies of Pain. In: *Bonica's Management of Pain.* 4th ed. Lippincott Williams & Wilkins; 2009:13-23.

8. International Association for the Study of Pain. IASP Taxonomy: Pain Terms. Available at: http://www.iasp-pain.org/Content/NavigationMenu/GeneralResourceLinks/PainDefinitions/default.htm. Accessed September 21, 2011.

9. Landmark T, Romundstad P, Borchgrevink PC, Kaasa S, Dale O. Associations between recreational exercise and chronic pain in the general population: Evidence from the HUNT 3 study. *Pain*. 2011.

10. Blyth FM, March LM, Brnabic a J, et al. Chronic pain in Australia: a prevalence study. *Pain*. 2001;89(2-3):127-34.

11. Elliott a M, Smith BH, Penny KI, Smith WC, Chambers W a. The epidemiology of chronic pain in the community. *Lancet*. 1999;354(9186):1248-52.

12. Eriksen J, Jensen MK, Sjøgren P, Ekholm O, Rasmussen NK. Epidemiology of chronic non-malignant pain in Denmark. *Pain*. 2003;106(3):221-228.

13. Rustøen T, Wahl AK, Hanestad BR, et al. Prevalence and characteristics of chronic pain in the general Norwegian population. *Eur J Pain*. 2004;8(6):555-65.

14. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur J Pain*. 2006;10(4):287-333.

15. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain*. 2009;10(2):113–130.

16. Pergolizzi J, Böger RH, Budd K, et al. Opioids and the management of chronic severe pain in the elderly: consensus statement of an International Expert Panel with focus on the six clinically most often used World Health Organization Step III opioids (buprenorphine, fentanyl, hydromorphone, met. *Pain Pract*. 2008;8(4):287-313.

17. Kalso E, Allan L, Dellemijn PLI, et al. Recommendations for using opioids in chronic non-cancer pain. *Eur J Pain*. 2003;7(5):381–386.

18. The British Pain Society. The British Pain Society ’s Opioids for persistent pain : Good practice. *Pain*. 2010;(January).

19. Vadivelu N, Urman RD, Hines RL eds. Acute and Chronic Mechanisms of Pain. In: *Essentials of Pain Management*. New York, NY: Springer New York; 2011:45-54.

20. Toblin RL, Mack K a, Perveen G, Paulozzi LJ. A population-based survey of chronic pain and its treatment with prescription drugs. *Pain*. 2011.

21. Moulin DE, Clark AJ, Speechley M, Morley-Forster PK. Chronic pain in Canada--prevalence, treatment, impact and the role of opioid analgesia. *Pain Res Manag*. 2002;7(4):179-84.

22. Eriksen J, Sjøgren P, Bruera E, Ekholm O, Rasmussen NK. Critical issues on opioids in chronic non-cancer pain: an epidemiological study. *Pain*. 2006;125(1-2):172-9.

23. Fishman SM, Ballantyne JC, Rathmell JP eds. Interdisciplinary Chronic Pain Management: Perspectives on History, Current Status and Future Viability. In: *Bonica’s Management of Pain.* 4th ed. Lippincott Williams & Wilkins; 2009:1523-32.

24. Waldman SD ed. *Pain Management*. 2nd ed. Elsevier Saunders

25. Rang HP, Dale MM, Ritter JM, Flower RJ, Henderson G. *Rang and Dale’s Pharmacology*. 7th ed. Elsevier Churchill Livingstone; 2012.

26. Wall PD, Melzack R, McMahon SB, Koltzenburg M. *Wall and Melzack’s textbook of pain*. Philadelphia: Elsevier Churchill Livingstone; 2006:XVIII, 1239 s.

27. Goodman LS. *Goodman & Gilman’s the pharmacological basis of therapeutics*. (Hardman JG, Limbird L, Gilman A, Rall TR, eds.). McGraw-Hill; 2001:1841.

28. Vadivelu N, Urman RD, Hines RL eds. Opioids: Pharmacokinetics and Pharmacodynamics. In: *Essentials of Pain Management*. New York, NY: Springer New York; 2011:91-103.

29. Prioreschi P, Heaney RP, Brehm E. A quantitative assessment of ancient therapeutics: poppy and pain in the Hippocratic Corpus. *Med Hypotheses*. 1998;51(4):325-31.

30. Macht DI. The History of opium and some of its preparations and alkaloids. *JAMA*. 1915;64(6):477-481.

31. Sneader W. The discovery of heroin. *Lancet*. 1998;352(9141):1697-9.

32. International Narcotics Control Board. INCB Mandate and Functions. Available at: http://www.incb.org/incb/mandate.html. Accessed September 30, 2011.

33. Chesneaux J, Bastid M, Bergeré M-C. *China from the Opium Wars to the 1911 revolution*. The Harvester Press ltd. 1977.

34. United Nations. *Single Convention on Narcotic Drugs, 1961, as ammended 1972.* 1972.

35. International Narcotics Control Board. Annual Report. 2010. Available at: http://www.incb.org/pdf/annual-report/2010/en/AR_2010_English.pdf. Accessed October 10, 2011.

36. Aronson JK ed. *Meyler's Side Effects of Drugs*. 15th ed. Elsevier; 2006:2619-2639.

37. Christie MJ. Cellular neuroadaptations to chronic opioids: tolerance, withdrawal and addiction. *Br J Pharmacol*. 2008;154(2):384-96.

38. Fernandes LC, Kilicarslan T, Kaplan HL, et al. Treatment of codeine dependence with inhibitors of cytochrome P450 2D6. *J Clin Psychopharmacol*. 2002;22(3):326-9.

39. Højsted J, Sjøgren P. Addiction to opioids in chronic pain patients: a literature review. *Eur J Pain*. 2007;11(5):490-518.

40. Ballantyne JC, LaForge KS. Opioid dependence and addiction during opioid treatment of chronic pain. *Pain*. 2007;129(3):235-55.

41. Savage SR. Assessment for addiction in pain-treatment settings. *Clin J Pain*. 2002;18(4 Suppl):S28-38.

42. Portenoy RK. Chronic opioid therapy in nonmalignant pain. *J Pain Symptom Manage*. 1990;5(1 Suppl):S46-62.

43. Chabal C, Erjavec MK, Jacobson L, Mariano A, Chaney E. Prescription opiate abuse in chronic pain patients: clinical criteria, incidence, and predictors. *Clin J Pain*. 1997;13(2):150-5.

44. Fishbain D a, Cole B, Lewis J, Rosomoff HL, Rosomoff RS. What percentage of chronic nonmalignant pain patients exposed to chronic opioid analgesic therapy develop abuse/addiction and/or aberrant drug-related behaviors? A structured evidence-based review. *Pain Med*. 2008;9(4):444-59.

45. Edlund MJ, Sullivan M, Steffick D, Harris KM, Wells KB. Do users of regularly prescribed opioids have higher rates of substance use problems than nonusers? *Pain Med*. 2007;8(8):647-56.

46. Højsted J, Nielsen PR, Guldstrand SK, Frich L, Sjøgren P. Classification and identification of opioid addiction in chronic pain patients. *Eur J Pain*. 2010;14(10):1014-20.

47. National Opioid Use Guideline Group (NOUGG). Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain. 2010. Available at: http://nationalpaincentre.mcmaster.ca/opioid/. Accessed October 10, 2011.

48. Statens Legemiddelverk. *Bruk av opioider ved behandling av langvarige , non-maligne smertetilstander - en oppdatering*. 2008.

49. Hanks GW, Conno F, Cherny N, et al. Morphine and alternative opioids in cancer pain: the EAPC recommendations. *Br J Cancer*. 2001;84(5):587-93.

50. Rothman KJ. *Modern Epidemiology*. 1st ed. Little, Brown and Company; 1986.

51. Strom BL ed. *Pharmacoepidemiology*. Chichester, UK: John Wiley & Sons, Ltd; 2006.

52. Andersohn F, Garbe E. [Pharmacoepidemiological research with large health databases]. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz*. 2008;51(10):1135-44.

53. International Narcotics Control Board. Narcotic Drugs - Technical Report. 2010. Available at: http://www.incb.org/pdf/technical-reports/narcotic-drugs/2010/Narcotic_drugs_publication_2010.pdf. Accessed September 30, 2011.

54. Pain and Policy Study Group. Opioid Consumption Motion Chart. 2011. Available at: http://ppsg-production.heroku.com/chart. Accessed September 24, 2011.

55. Fredheim OMS, Skurtveit S, Breivik H, Borchgrevink PC. Increasing use of opioids from 2004 to 2007 - pharmacoepidemiological data from a complete national prescription database in Norway. *Eur J Pain*. 2010;14(3):289-294.

56. Olsen Y, Daumit GL, Ford DE. Opioid prescriptions by U.S. primary care physicians from 1992 to 2001. *J Pain*. 2006;7(4):225-35.

57. Caudill-Slosberg M a, Schwartz LM, Woloshin S. Office visits and analgesic prescriptions for musculoskeletal pain in US: 1980 vs. 2000. *Pain*. 2004;109(3):514-9.

58. Boudreau DM, Von Korff M, Rutter CM, et al. Trends in long-term opioid therapy for chronic non-cancer pain. *Pharmacoepidemiol Drug Saf*. 2009;18(12):1166-75.

59. Porucznik CA, Sauer BC, Johnson EM, et al. Morbidity and Mortality Weekly Report Adult Use of Prescription Opioid Pain Medications — Utah , 2008. *Morbidity And Mortality Weekly Report CDC*. 2010;59(6):153-7.

60. Franklin GM, Mai J, Wickizer T, et al. Opioid dosing trends and mortality in Washington State workers' compensation, 1996-2002. *Am J Ind Med*. 2005;48(2):91-9.

61. Haydon E, Rehm J, Fischer B, Monga N, Adlaf E. Prescription drug abuse in Canada and the diversion of prescription drugs into the illicit drug market. *Can J Public Health*. 2005;96(6):459-61.

62. Buckeridge D, Huang A, Hanley J, et al. Risk of injury associated with opioid use in older adults. *J Am Geriatr Soc*. 2010;58(9):1664-70.

63. De Conno F, Ripamonti C, Brunelli C. Opioid purchases and expenditure in nine western European countries: "Are we killing off morphine?" *Pall Med*. 2005;19(3):179-184.

64. Hamunen K, Laitinen-Parkkonen P, Paakkari P, et al. What do different databases tell about the use of opioids in seven European countries in 2002? *Eur J Pain*. 2008;12(6):705-15.

65. Hamunen K, Paakkari P, Kalso E. Trends in opioid consumption in the Nordic countries 2002-2006. *Eur J Pain*. 2009;13(9):954-62.

66. Groth Clausen T, Eriksen J, Borgbjerg FM. Legal opioid consumption in Denmark 1981-1993. *Eur J Clin Pharmacol*. 1995;48(5):321-5.

67. Jarlbaek L, Kehlet H, Sjøgren P. [The licit opioid consumption in Denmark]. *Ugeskrift for laeger*. 2010;172(46):3173-8.

68. Jarlbaek L, Andersen M, Hallas J, Engholm G, Kragstrup J. Use of opioids in a Danish population-based cohort of cancer patients. *J Pain Symptom Manage*. 2005;29(4):336-43.

69. Jarlbaek L, Hallas J, Kragstrup J, Andersen M. Cancer patients' first treatment episode with opioids: a pharmaco-epidemiological perspective. *Support Care Cancer*. 2006;14(4):340-7.

70. Jarlbaek L, Andersen M, Kragstrup J, Hallas J. Cancer patients' share in a population's Use of opioids. A linkage study between a prescription database and the danish cancer registry. *J Pain Symptom Manage*. 2004;27(1):36-43.

71. Garcia del Pozo J, Carvajal A, Viloria JM, Velasco A, Garcia del Pozo V. Trends in the consumption of opioid analgesics in Spain. Higher increases as fentanyl replaces morphine. *Eur J Clin Pharmacol*. 2008;64(4):411-5.

72. Pokela N, Bell JS, Lihavainen K, Sulkava R, Hartikainen S. Analgesic use among community-dwelling people aged 75 years and older: A population-based interview study. *The American journal of geriatric pharmacotherapy*. 2010;8(3):233-44.

73. Bell JS, Laitinen M-L, Lavikainen PT, et al. Use of strong opioids among community-dwelling persons with and without Alzheimer's disease in Finland. *Pain*. 2011;152(3):543-7.

74. Hudec R, Tisonová J, Bozeková L, Foltán V. Trends in consumption of opioid analgesics in Slovak Republic during 1998-2002. *Eur J Clin Pharmacol*. 2004;60(6):445-8.

75. Bergman U. The history of the Drug Utilization Research Group in Europe. *Pharmacoepidemiol Drug Saf*. 2006;15(2):95-8.

76. Eggen AE, Andrew M. Use of codeine analgesics in a general population. A Norwegian study of moderately strong analgesics. *Eur J Clin Pharmacol*. 1994;46(6):491-6.

77. Dybwad TB, Sundene G, Eskerud J, Hjortdahl P, Matheson I. [Control of prescriptions of B-preparations. A registry study of B-preparations in Oslo and Akershus]. *Tidsskr Nor Laegeforen*. 1994;114(27):3207-10.

78. Engeland A, Skurtveit S, Mørland J. Risk of road traffic accidents associated with the prescription of drugs: a registry-based cohort study. *Ann Epidemiol*. 2007;17(8):597-602.

79. Bramness JG, Kornør H. Benzodiazepine prescription for patients in opioid maintenance treatment in Norway. *Drug Alcohol Depend*. 2007;90(2-3):203-9.

80. Bachs LC, Bramness JG, Engeland A, Skurtveit S. Repeated dispensing of codeine is associated with high consumption of benzodiazepines. *Nor J Epidemiol*. 2008;18(2):185-190.

81. Skurtveit S, Furu K, Bramness JG, Tverdal A. Benzodiazepine use in all alcohol consumers predicts use of opioids in patients 20 years later--a follow-up study of

13,390 men and women aged 40-42 years. *Pharmacoepidemiol Drug Saf*. 2008;17(9):926-933.

82. Fredheim OMS, Skurtveit S, Moroz A, Breivik H, Borchgrevink PC. Prescription pattern of codeine for non-malignant pain: a pharmacoepidemiological study from the Norwegian Prescription Database. *Acta anaesthesiol Scand*. 2009;53(5):627-33.

83. Skurtveit S, Furu K, Kaasa S, Borchgrevink PC. Introduction of low dose transdermal buprenorphine -- did it influence use of potentially addictive drugs in chronic non-malignant pain patients? *Eur J Pain*. 2009;13(9):949-53.

84. Bachs LC, Engeland A, Mørland JG, Skurtveit S. The risk of motor vehicle accidents involving drivers with prescriptions for codeine or tramadol. *Clin Pharmacol Ther*. 2009;85(6):596-9.

85. Skurtveit S, Furu K, Bramness JG, Selmer R, Tverdal A. Benzodiazepines predict use of opioids--a follow-up study of 17,074 men and women. *Pain Med*. 2010;11(6):805-14.

86. Skurtveit S, Furu K, Selmer R, Handal M, Tverdal A. Nicotine dependence predicts repeated use of prescribed opioids. Prospective population-based cohort study. *Ann Epidemiol*. 2010;20(12):890-7.

87. Fredheim OMS, Log T, Olsen W, et al. Prescriptions of opioids to children and adolescents; a study from a national prescription database in Norway. *Paediatr Anaesth*. 2010;20(6):537-44.

88. Fredheim OMS, Borchgrevink PC, Nordstrand B, Clausen T, Skurtveit S. Prescription of analgesics to patients in opioid maintenance therapy: a pharmacoepidemiological study. *Drug Alcohol Depend*. 2011;116(1-3):158-62.

89. Fredheim OMS, Moksnes K, Borchgrevink PC, Skurtveit S. Opioid switching to methadone: a pharmacoepidemiological study from a national prescription database. *Pall Med*. 2011.

90. Handal M, Engeland A, Rønning M, Skurtveit S, Furu K. Use of prescribed opioid analgesics and co-medication with benzodiazepines in women before, during, and after pregnancy: a population-based cohort study. *Eur J Clin Pharmacol*. 2011;67(9):953-60.

91. Log T, Hartz I, Handal M, et al. The association between smoking and subsequent repeated use of prescribed opioids among adolescents and young adults--a population-based cohort study. *Pharmacoepidemiol Drug Saf*. 2011;20(1):90-8.

92. Log T, Skurtveit S, Tverdal A, Furu K, Hartz I. Dispensing of prescribed analgesics in Norway among young people with foreign- or Norwegian-born parents. *Scandinavian Journal of Pain*. 2011;2(1):36-44.

93. Skurtveit S, Furu K, Borchgrevink PC, Handal M, Fredheim OMS. To what extent does a cohort of new users of weak opioids develop persistent or probable problematic opioid use? *Pain*. 2011.

94. Ineke Neutel C, Skurtveit S, Berg C. Polypharmacy of potentially addictive medication in the older persons-quantifying usage. *Pharmacoepidemiol Drug Saf*. 2011.

95. Nordbø A, Skurtveit S, Borchgrevink PC, Kaasa S, Fredheim OMS. Low-dose transdermal buprenorphine - long-term use and co-medication with other potentially addictive drugs. *Acta anaesthesiol Scand*. 2011:n/a-n/a.

96. Helland A, Spigset O, Slørdal L. [Problem forte--is paracetamol-codeine combination rational?]. *Tidsskr Nor Laegeforen*. 2004;124(16):2084-7.

97. Gardarsdottir H, Heerdink ER, Egberts ACG. Potential bias in pharmacoepidemiological studies due to the length of the drug free period: a study on antidepressant drug use in adults in the Netherlands. *Pharmacoepidemiol Drug Saf*. 2006;15(5):338-43.

98. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment. 2010. Available at: http://www.whocc.no. Accessed May 10, 2011.

99. Rønning M, Salvesen Blix H, Tange Harbø B, Strøm H. Different versions of the anatomical therapeutic chemical classification system and the defined daily dose - are drug utilisation data comparable? *Eur J Clin Pharmacol*. 2000;56(9):723-727.

100. Curry EA, Palla S, Hung F, Arbuckle R, Bruera E. Prescribing patterns and purchasing costs of long-acting opioids over nine years at an academic oncology hospital. *Am J Health Syst Pharm*. 2007;64(15):1619-25.

101. Gardarsdottir H, Souverein PC, Egberts TCG, Heerdink ER. Construction of drug treatment episodes from drug-dispensing histories is influenced by the gap length. *J Clin Epidemiol*. 2010;63(4):422-7.

102. Furu K. Establishment of the nationwide Norwegian Prescription Database (NorPD) – new opportunities for research in pharmacoepidemiology in Norway. *Nor J Epidemiol*. 2008;18(2):129-136.

103. Furu K, Wettermark B, Andersen M, et al. The Nordic countries as a cohort for pharmacoepidemiological research. *Basic Clin Pharmacol Toxicol*. 2010;106(2):86-94.

104. Norwegian Institute of Public Health. Norwegian Prescription Registry. Available at: http://www.norpd.no/. Accessed September 20, 2011.

105. Norwegian Tax Administration. Fødselsnummer [Personal Identification Number]. Available at: http://www.skatteetaten.no/no/Alt-om/Folkeregistrering/Fodselsnummer/. Accessed September 20, 2011.

106. Utne H. The Population and Housing Census Handbook 2001. Available at: http://www.ssb.no/english/subjects/02/01/doc_200502_en/doc_200502_en.pdf. Accessed September 20, 2011.

107. Hammer H. [The central population registry in medical research]. *Tidsskr Nor Laegeforen*. 2002;122(26):2550.

108. Statistics Norway. StatBank Norway. Available at: http://statbank.ssb.no//statistikkbanken/default_fr.asp?PLanguage=1. Accessed September 20, 2011.

109. Klepstad P, Borchgrevink PC, Kaasa S. Effects on cancer patients' health-related quality of life after the start of morphine therapy. *J Pain Symptom Manage*. 2000;20(1):19-26.

110. Norwegian Medicines Agency. Summary of product characteristics, Ketorax. Available at: http://www.legemiddelverket.no/custom/Preparatsok/prepSearch___80333.aspx. Accessed September 21, 2011.

111. Norwegian Medicines Agency. Summary of product characteristics, Actiq. Available at: http://www.legemiddelverket.no/custom/Preparatsok/prepSearch___80333.aspx. Accessed September 21, 2011.

112. Back I. Palliative Care Guidelines Plus. Available at: http://book.pallcare.info/index.php?tid=125&dg=8. Accessed January 15, 2009.

113. Souter K, Fitzgibbon D. Equianalgesic dose guidelines for long-term opioid use: Theoretical and practical considerations. *Seminars in Anesthesia, Perioperative Medicine and Pain*. 2004;23(4):271-280.

114. Sittl R, Likar R, Nautrup BP. Equipotent doses of transdermal fentanyl and transdermal buprenorphine in patients with cancer and noncancer pain: results of a retrospective cohort study. *Clin Ther*. 2005;27(2):225-37.

115. Patanwala AE, Duby J, Waters D, Erstad BL. Opioid conversions in acute care. *Ann Pharmacother*. 2007;41(2):255-66.

116. Divvela S, Williams A, Meives C, Gozun E. opioid analgesics: comparison of pharmacokinetics and equianalgesic doses. *Hosp Pharm*. 2006;42(11):1130-1135.

117. Anderson R, Saiers JH, Abram S, Schlicht C. Accuracy in equianalgesic dosing. conversion dilemmas. *J Pain Symptom Manage*. 2001;21(5):397-406.

118. Ohqvist G, Hallin R, Gelinder S, Lang H, Samuelson S. A comparison between morphine, meperidine and ketobemidone in continuous intravenous infusion for postoperative relief. *Acta anaesthesiol Scand*. 1991;35(1):44-8.

119. MacAuley D. Narcotic analgesic converter. Available at: http://www.globalrph.com/narcotic.cgi. Accessed October 3, 2011.

120. Hallas J. Drug utilization statistics for individual-level pharmacy dispensing data. *Pharmacoepidemiol Drug Saf*. 2005;14(7):455-63.

121. Hallas J, Gaist D, Bjerrum L. The waiting time distribution as a graphical approach to epidemiologic measures of drug utilization. *Epidemiology*. 1997;8(6):666-70.

122. Støvring H, Vach W. Estimation of prevalence and incidence based on occurrence of health-related events. *Stat Med*. 2005;24(20):3139-54.

123. Hallas J, Støvring H. Templates for analysis of individual-level prescription data. *Basic Clin Pharmacol Toxicol*. 2006;98(3):260-5.

124. OECD Project on Income Distribution and Poverty. What are equivalence scales? 2008. Available at: http://www.oecd.org/dataoecd/61/52/35411111.pdf. Accessed July 1, 2011.

125. International Organization for Standardization. What is ISO 3166? Available at: http://www.iso.org/iso/country_codes/background_on_iso_3166/what_is_iso_3166.htm. Accessed October 10, 2011.

126. Anon. Magic Maps. Available at: http://magicmaps.evanmiller.org/. Accessed November 22, 2011.

127. Volinn E, Fargo JD, Fine PG. Opioid therapy for nonspecific low back pain and the outcome of chronic work loss. *Pain*. 2009;142(3):194-201.

128. Rigler SK, Shireman TI, Kallenbach L. Predictors of long-acting opioid use and oral versus transdermal route among older Medicaid beneficiaries. *Am J Geriatr Pharmacother*. 2007;5(2):91-9.

129. Stover BD, Turner J a, Franklin G, et al. Factors associated with early opioid prescription among workers with low back injuries. *J Pain*. 2006;7(10):718-25.

130. Edlund MJ, Steffick D, Hudson T, Harris KM, Sullivan M. Risk factors for clinically recognized opioid abuse and dependence among veterans using opioids for chronic non-cancer pain. *Pain*. 2007;129(3):355-62.

131. Dosa DM, Dore DD, Mor V, Teno JM. Frequency of long-acting opioid analgesic initiation in opioid-naïve nursing home residents. *J Pain Symptom Manage*. 2009;38(4):515-21.

132. Suissa S, Garbe E. Primer: administrative health databases in observational studies of drug effects--advantages and disadvantages. *Nat Clin Pract Rheumatol*. 2007;3(12):725-32.

133. Bakken IJ, Estenstad MG, Gystad SO, Németh J, Huse E. Nytt Norsk pasientregister gir nye forskningsmuligheter. *Nor J Epidemiol*. 2010;20(april 2009):119-124.

134. Parsells Kelly J, Cook SF, Kaufman DW, et al. Prevalence and characteristics of opioid use in the US adult population. *Pain*. 2008;138(3):507-13.

135. Helin-Salmivaara A, Lavikainen PT, Korhonen MJ, et al. Pattern of statin use among 10 cohorts of new users from 1995 to 2004: a register-based nationwide study. *Am J Manag Care*. 2010;16(2):116-22.

136. Sawada N, Uchida H, Suzuki T, et al. Persistence and compliance to antidepressant treatment in patients with depression: a chart review. *BMC psychiatry*. 2009;9:38.

137. Corrao G, Parodi A, Zambon A, et al. Reduced discontinuation of antihypertensive treatment by two-drug combination as first step. Evidence from daily life practice. *J Hypertens*. 2010;28(7):1584-90.

138. Organisation for Economic Co-operation and Development. Employment and Labour Markets: Key Tables from OECD. 2011. Available at: http://www.oecd-ilibrary.org/employment/employment-and-labour-markets-key-tables-from-oecd_20752342;jsessionid=8brbgsis4f09s.delta. Accessed October 31, 2011.

139. Hargreave M, Andersen TV, Nielsen A, et al. Factors associated with a continuous regular analgesic use - a population-based study of more than 45,000

Danish women and men 18-45 years of age. *Pharmacoepidemiol Drug Saf*. 2010;19(1):65-74.

140. Chase DM, Rincon A, Deane M, Tewari KS, Brewster WR. Socioeconomic factors may contribute to neoadjuvant chemotherapy use in metastatic epithelial ovarian carcinoma. *Gynecol Oncol*. 2009;115(3):339-42.

141. Norwegian Pharmacy Association. *Apotek og Legemidler 2011*. Oslo; 2011.

142. Rønning M, Berg C, Furu K, et al. *Legemiddelstatistikk 2010:2. Topic: Addictive drugs*. 2010.

143. Haugen O, Hjort PF, Waaler HT. [Different drug consumption in the counties, different medical and economical consequences? A statistical analysis of drug consumption in Norway]. *Tidsskr Nor Laegeforen*. 1978;98(31):1546-7.

Paper I

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Paper II

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Paper III

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Appendix

DIFFERENT USEFUL STATA CODES

The syntax for Stata 11 will be shown and commented on. Before moving on to this however it is important to understand how the syntax here is colour coded and built up. Firstly all text in red are comments and Stata knows to overlook all lines starting with * and all text enclosed by /* and */. It is used actively to explain what the different macros that are being defined means below. Next all text in underlined green and blue are commands. For instance the text local as seen frequently in the syntax defines a macro with a name (first word after local) and content (the rest of the text after local and the macro name). It is not appropriate to go into details how macros and other programming concepts work, but a good reference to read is "The Workflow of Data Analysis Using Stata" (108). The next colour used is **bright blue and bold**, this is macros being recalled and used in commands. For dark blue as seen in { and } is the start of and end of a loop. Pink are operators such as = and : used in assignment and specifying commands. The final colour used is brown, meaning text used as a string. An operator in brown for instance will be read as it is, not as an assignment.

OMEQ

Using a data file with dispensed prescriptions it is first necessary to create macros with the variables to be inputted in the syntax. For this syntax five variables are needed, the ATC code of each prescription, the product number of each pack dispensed, the date the prescription was dispensed and the number of DDDs that was dispensed. Finally the patient ID number is needed (line 4) to later create the persistent use definitions.

```
1  local ATCKode /* variable for ATC-Code here PS: the letters in the ATC-codes needs to be capitalized!*/
2  local VareNr /* variable for product number here */
3  local UtleveringsDato /* variable for date of dispensing*/
4  local PasientLopeNr /* variable for patient ID*/
5  local OrdinasjonAntallDDD /* variable for DDD per prescription dispensed*/
```

Then in line 6-14 the equianalgesic ratios are coded in for each prescription. This is done by running a loop (line 10-14) recoding each ATC-code (line 7) to the corresponding equianalgesic ratios (line 8)

```
6  generate MEQFAC = .
7  local meqfac_atc N02AB01 N02AB02 N02AA59 N02AB03 N02AC54 N02AD01
   N02AE01 N02AA01 N02AG01 N02AG02 N02AA03 N02AA08 N02AA05 N02AX02
8  local meqfac_pot 3 0.1 0.15 100 0.15 0.17 110 1 1 3 6 0.13 1.5 0.2
9  local counter =0
10 foreach atc in `meqfac_atc' {
11     local ++counter
12     local potens : word `counter' of `meqfac_pot'
13     recode MEQFAC (.=`potens') if `ATCKode'=="`atc'"
14 }
```

The matter becomes more complicated as each ATC code can have more than one equianalgesic ratio. This is due to the different administration forms some opioids have and the different bioavailability of these forms. Using the product number these administration forms are coded with a ratio comparing their equianalgesic ratio to the main ratio for that opioid (line 15-16). In order to calculate the mg OMEQ per prescription the defined daily dose (DDD) has to be used, in line 17-26 the DDD (line 19) is coded for each ATC code (line 18). This is accomplished using a loop as done for the equianalgesic ratios.

```
15 gen admin_faktor =  `VareNr'
16 recode admin_faktor (267351=1.4)(20944 20955 267606=1.5)(496729 496737
   266452 496935=0.33)(14860 329664 11437 11866 12997 13904 14225 329409
   449298 551721 360734=3)(6289 6466 6512 6543 6328 6336 6369 6380 6413
   6422 6455 6499=0.5)(65466 522441 1628=0.45)(else=1)
17 generate DDD_fra_atc = .
18 local ddd_atc N02AB01 N02AB02 N02AC54 N02AD01 N02AE01 N02AG01 N02AG02
   N02AA03 N02AA08 N02AX02
19 local ddd_mg 50 400 140 200 1.2 10 25 20 150 300
20 local counter =0
21 foreach atc in `ddd_atc' {
22     local ++counter
23     local potens : word `counter' of `ddd_mg'
24     recode DDD_fra_atc (.=`potens') if `ATCKode'=="`atc'"
25 }
26 recode DDD_fra_atc (.=1)
```

The DDD has the same problem as in the equianalgesic rations, with each ATC code having more than one DDD the product code is also here used in coding the DDD doses for all opioids with more than one DDD. This is shown in line 27-35, with line 34 creating a variable and line 35 recoding the variable using the macros created in line 27-33.

```
27  local DDD_pinex_forte 69302 69310 69328 69344 69351 2979 453878 487256
    544080 578419 /* codeine */
28  local DDD_paral_forte 112664 112672 112680 112698 112706 116822 116830
    119099 119107 119109 119115 189274 266619 281998 389353 575381 583526/*
    codeine */
29  local DDD_oksykodon_tbl 3337 3404 3413 3415 3439 13346 5604 5706 5715
    5731 5739 5750 5773 5798 5842 6729 6741 6772 9521 9532 9543 9554 9565
    9576 9587 9598 13346 3371 3428
30  local DDD_morfoks_inj 329409 329664 11437 11866 12997 13904 14225
    449298 551721 20944 20955 267606 /* morphine & oxycodone injections both same
    DDD*/
31  local DDD_fentanyl_tm 6289 6328 6336 6369 6380 6413 6422 6455 6466 6499
    6512 6543  /* transmucosal/sublingual fentanyl*/
32  local DDD_fentanyl_td 18995 19094 19108 19167 22353 22375 22389 22411
    24056 60114 60123 60150 60159 60168 60177 60187 103806 60132 60141
    451328 451369 451385 451401 /* transdermal fentanyl*/
33  local DDD_morfin_tbl 27904 28811 139881 286209 424036 424549 424614
    424804 461400 461434 478685 478743 478834 478875 488734 551739 551747
    551754 551796 563767 581983 /* morphine tablets*/
34
    generate DDD_fra_vnr =  `VareNr'
35  recode DDD_fra_vnr ( `DDD_pinex_forte'=90) ( `DDD_paralgin_forte'=120)
    ( `DDD_oksykodon_tbl'=75) ( `DDD_morfoks_inj'=30) ( `DDD_fentanyl_tm' =
    0.6) ( `DDD_fentanyl_td'=1.2) ( `DDD_morfin_tbl'=100)(else=1)
```

The final step of creating the OMEQ variable is to multiply the equianalgesic ratio created in line 10-14 with the administration factor created in line 15-16 and with the DDD created in line 21-26 and the DDD from product numbers in line 34-35. This is done in line 37, but before that line 36 creates a cross table of the variables DDD from ATC and DDD from product number, here no dispensed prescriptions should have the value 1 in both, if so, something is wrong and probably some product numbers have not been recoded as they should have been. The 6 final lines in the code, line 28-44 are inserting labels to the variables just created.

```
36  table  DDD_fra_atc DDD_fra_vnr
37  gen konverteringsfaktor  = MEQFAC* admin_faktor* DDD_fra_atc*
    DDD_fra_vnr
38  gen OMEQ =  konverteringsfaktor* `OrdinasjonAntallDDD'
39  label var OMEQ "mg oral morphine equivalents per prescription"
40  label var konverteringsfaktor "factor to multiply DDD with"
41  label var DDD_fra_vnr "DDD in mg from product code"
42  label var DDD_fra_atc "DDD in mg from ATC"
43  label var admin_faktor "factor between different administration forms"
44  label var MEQFAC "equianalgesic ratio between opioid and oral morphine"
```

Definitions of persistent opioid use

This part of the code should be run when running the OMEQ code. This is because the macros defining the names of variables inputted are not repeated here, if this code is to be run separately the same five lines as in the beginning of the OMEQ code needs to be inserted before line 1 here. The first 4 lines in this syntax created the first date of prescription dispensed for each patients using the egen command with the bysort prefix (line 1) then for each prescription dispensed the number of days from the first prescription is created (line 3) and if the gap is longer than 365 days the prescription is removed (line 4) since the persistent opioid use definitions measure use during 365 days after first prescription dispensed in a year.

```
1  bysort  `PasientLopeNr': egen forstedato = min( `UtleveringsDato' )
```

```
2  format forstedato %td
3  gen gap =  `UtleveringsDato'- forstedato
4  drop if  gap>365
```

Then for each prescription dispensed the corresponding quarter of the 365 day study period is coded (line 5-9) and in order to count the number of quarters opioids are dispensed lines 10 to 18 is needed. Line 19 counts number of prescriptions dispensed per patient and line 20-24 drops all temporary variables created in these steps and labels the remaining variables .

```
5  gen kvartal =0
6  recode kvartal (0=1) if gap<91
7  recode kvartal (0=2) if gap<181
8  recode kvartal (0=3) if gap<271
9  recode kvartal (0=4) if gap<366
10 egen kvartal1 = anymatch( kvartal), v(1)
11 egen kvartal2 = anymatch( kvartal), v(2)
12 egen kvartal3 = anymatch( kvartal), v(3)
13 egen kvartal4 = anymatch( kvartal), v(4)
14 by  `PasientLopeNr': egen k1max = max( kvartal1)
15 by  `PasientLopeNr': egen k2max = max( kvartal2)
16 by  `PasientLopeNr': egen k3max = max( kvartal3)
17 by  `PasientLopeNr': egen k4max = max( kvartal4)
18 egen qtrs = rowtotal( k1max k2max k3max k4max)
19 by  `PasientLopeNr': egen resepter= count( gap)
20 drop k4max k3max k2max k1max kvartal4 kvartal3 kvartal2 kvartal1
   kvartal
21 lab var resepter "number of dispensed prescriptions in 365 days"
22 lab var qtrs "number of quarters of the year with opioids dispensed"
23 lab var forstedato "first date of dispension"
24 lab var gap "time from first dispension"
```

Line 25 deserves some attention, the collapse command highlighted in yellow is special because it is destructive. It will aggregate the prescription data to patient data, and as there are no ”undo” function caution is needed. Always save the data, or use the preserve command if one is not absolutely sure that the command is set up exactly as it should. When collapsing the data, the first date of dispensing, the number of quarters and number of prescriptions are carried on

into the patient file, in addition the total amount of opioids dispensed in DDD and OMEQ for each patient are created.

```
25  collapse (mean) forstedato qtrs resepter (sum) OMEQtot=OMEQ
    DDDtot=`OrdinasjonAntallDDD', by(`PasientLopeNr')
```

Finally the definitions can be created first by making binary variables for the different dimensions to be used, for number of quarters of the 365 day period (line 26-39), amounts of opioid in OMEQ (line 30-35) and DDD (line 36-41) and number of prescriptions (line 42-43). The two different opioid amount variables are combined in line 44-46 and the strict (line 47-48), intermediary (line 49-59) and wide (line 51-52) definitions are coded as binary variables by combining the dimensions.

```
26  gen qtrs4 = 0
27  recode  qtrs4 (0=1) if qtrs==4
28  gen qtrs3 = 0
29  recode  qtrs3 (0=1) if qtrs>=3
30  gen OMEQ18000 = 0
31  recode  OMEQ18000 (0=1) if  OMEQtot>=18000
32  gen OMEQ9000 = 0
33  recode  OMEQ9000 (0=1) if  OMEQtot>=9000
34  gen OMEQ4500 = 0
35  recode  OMEQ4500 (0=1) if  OMEQtot>=4500
36  gen DDD730 = 0
37  recode  DDD730 (0=1) if  DDDtot>=730
38  gen DDD365 = 0
39  recode  DDD365 (0=1) if  DDDtot>=365
40  gen DDD180 = 0
41  recode  DDD180 (0=1) if  DDDtot>=180
42  gen resepter10 = 0
43  recode resepter10 (0=1) if  resepter>=10
44  gen strictamount =  OMEQ18000+ DDD730
45  gen intermamount =  OMEQ9000+ DDD365
46  gen wideamount =  OMEQ4500+ DDD180
```

```
47  gen strict_def = 0
48  recode strict_def (0=1) if strictamount>=1 & resepter10==1 &
    qtrs4==1
49  gen intermediate_def = 0
50  recode intermediate_def (0=1) if intermamount>=1 & qtrs4==1
51  gen wide_def = 0
52  recode wide_def (0=1) if wideamount>=1 & qtrs3==1
```

Figure 2 in paper III

The first part (line 1-9) is assigning different macros used later, the advantage is that when changing the code for graphing a different independent variable or for a different project, these 9 macros are the only ones needed to be changed. The explanation for each macro can be seen in red.

```
1  local depvar intermaar1                          /* dependent variable*/
2  local indepvar samlivsstatus                     /* independent variable*/
3  local referansekategori 2                        /* what value should be the reference (OR=1)*/
4  local kkat = 4                                   /* number of values in independent variable */
5  local modifier work_status                       /* effect modifier variable */
6  local kstrata = 3                                /* number of values in the effect modifier */
7  local if "if female==0 & alder67==0"             /* defining subpopulation to graph*/
8  local xaksenavn Marital status                   /* name on x-axis */
9  local farge "gs4 gs8 gs12 gs16"                  /* colours to be used on vertical graphs*/
```

The next four lines (line 10-13) are 4 empty macros being defined. These contain nothing now, but will become filled later on, and they need to be defined before entering loops.

```
10  local adj ""
11  local unadj ""
12  local tw ""
13  local xlabel ""
```

The next seven lines below (line 14-20) are used to create the labels to be used in the graph to name the categories of the independent variable line 14 is merely a counting macro, line 15 extracts the value labels from the independent variable and stores it in a macro. Line 16-20 is a short loop creating the correct syntax to use as the label, firstly the value for each category and then the corresponding label text this gets stored in a macro called xlabel and will be used in the final line of the syntax.

```
14  local irow = 1
15  local varlab : val lab `indepvar'
16  forvalues labnum = 1/`kkat' {
17      local vallab :lab `varlab' `irow'
18      local xlabel "`xlabel' `labnum' "`vallab'""
19      local ++irow
20  }
```

In this part the results from a logistic regression first without any effect modifier (line 23) and then stratified for the effect modifier (line 32) in a loop. The regression results gets extracted into macros that are combined in line 38 and 40 into a graphical command used to write lines between two points (the command is pci). As the loops run the results from each regression and each subcategory of the independent variable and effect modifying variable gets added to a single macro called tw.

```
21  quietly tabulate `indepvar'
22  local r = r(r)
23  quietly logistic `depvar' ib`referansekategori'.`indepvar' `if', base
24  matrix eb =e(b)
25  forvalues nummer = 1/`r' {
26      local b =eb[1,`nummer']
27      local exp = exp(`b')
28      local start = `nummer'-0.2
29      local slutt = `nummer'+0.2
30      local irow = 0
31      forvalues strata = 1/`kstrata' {
32          quietly logistic `depvar' ib`referansekategori'.`indepvar'
`if' &
            `modifier'==`strata' , base
33          matrix aeb = e(b)
34          local ++irow
35          local ab =aeb[1,`nummer']
36          local aexp = exp(`ab')
37          local lc : word `irow' of `farge'
38          local tw "`tw' (pci `exp' `x3' `aexp' `x3', lc(`lc')
lw(vvthick))"
39      }
40      local tw "`tw' (pci `exp' `start' `exp' `slutt', lc(black)
lw(vthick)
        lst(foreground))"
41  }
```

The macro `` `tw' `` is used to draw the graph and combined with different necessary options in line 42.

```
42  twoway `tw' ,legend(on order(1 2 3 4)label(1 "disability pension")
    label(2 "not working") label(3 "working") label(4 "unadjusted") cols(1)
    rowgap(2)keygap(3) symxsize(5) position(6) )
    ytitle("Oddsratio for being persistent opioid user") /* xtitle("`xaksenavn'")*/
    xtitle("") yline(1, lc(black))
    /* title("the modifying effect of `modifier' on `indepvar'") sub("`if'") */
    graphr(c(white))xlabel(`xlabel')
```

Dissertations at the Faculty of Medicine, NTNU

1977

1. Knut Joachim Berg: EFFECT OF ACETYLSALICYLIC ACID ON RENAL FUNCTION
2. Karl Erik Viken and Arne Ødegaard: STUDIES ON HUMAN MONOCYTES CULTURED *IN VITRO*

1978

3. Karel Bjørn Cyvin: CONGENITAL DISLOCATION OF THE HIP JOINT.
4. Alf O. Brubakk: METHODS FOR STUDYING FLOW DYNAMICS IN THE LEFT VENTRICLE AND THE AORTA IN MAN.

1979

5. Geirmund Unsgaard: CYTOSTATIC AND IMMUNOREGULATORY ABILITIES OF HUMAN BLOOD MONOCYTES CULTURED IN VITRO

1980

6. Størker Jørstad: URAEMIC TOXINS
7. Arne Olav Jenssen: SOME RHEOLOGICAL, CHEMICAL AND STRUCTURAL PROPERTIES OF MUCOID SPUTUM FROM PATIENTS WITH CHRONIC OBSTRUCTIVE BRONCHITIS

1981

8. Jens Hammerstrøm: CYTOSTATIC AND CYTOLYTIC ACTIVITY OF HUMAN MONOCYTES AND EFFUSION MACROPHAGES AGAINST TUMOR CELLS *IN VITRO*

1983

9. Tore Syversen: EFFECTS OF METHYLMERCURY ON RAT BRAIN PROTEIN.
10. Torbjørn Iversen: SQUAMOUS CELL CARCINOMA OF THE VULVA.

1984

11. Tor-Erik Widerøe: ASPECTS OF CONTINUOUS AMBULATORY PERITONEAL DIALYSIS.
12. Anton Hole: ALTERATIONS OF MONOCYTE AND LYMPHOCYTE FUNCTIONS IN REALTION TO SURGERY UNDER EPIDURAL OR GENERAL ANAESTHESIA.
13. Terje Terjesen: FRACTURE HEALING AND STRESS-PROTECTION AFTER METAL PLATE FIXATION AND EXTERNAL FIXATION.
14. Carsten Saunte: CLUSTER HEADACHE SYNDROME.
15. Inggard Lereim: TRAFFIC ACCIDENTS AND THEIR CONSEQUENCES.
16. Bjørn Magne Eggen: STUDIES IN CYTOTOXICITY IN HUMAN ADHERENT MONONUCLEAR BLOOD CELLS.
17. Trond Haug: FACTORS REGULATING BEHAVIORAL EFFECTS OG DRUGS.

1985

18. Sven Erik Gisvold: RESUSCITATION AFTER COMPLETE GLOBAL BRAIN ISCHEMIA.
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20. Lars Bevanger: STUDIES OF THE Ibc (c) PROTEIN ANTIGENS OF GROUP B STREPTOCOCCI.
21. Ole-Jan Iversen: RETROVIRUS-LIKE PARTICLES IN THE PATHOGENESIS OF PSORIASIS.
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23. Per I. Lundmo: ANDROGEN METABOLISM IN THE PROSTATE.

1986

24. Dagfinn Berntzen: ANALYSIS AND MANAGEMENT OF EXPERIMENTAL AND CLINICAL PAIN.
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1987

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28. Audun N. Øksendal: THE CALCIUM PARADOX AND THE HEART.
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1988

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1991

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1998

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1999

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2000

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159. xxxxxxxxx (blind number)
160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
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2001

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196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
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2002

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